

veins and lymphatics



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ABSTRACT BOOK

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5th Annual Meeting of the International Society for Neurovascular Disease

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KEYNOTE

THE HEART-BRAIN AXIS; AN OVERLOOKED CAUSE OF BRAIN AGING

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While both cardiac dysfunction and progressive loss of cognitive functioning are prominent features of an aging population, surprisingly few studies have addressed the link between heart and brain function. This is probably due to the monodisciplinary approach to these problems by cardiologists, neurologists and geriatricians. Recent data indicate that autoregulation of cerebral flow cannot always protect the brain from hypoperfusion when cardiac output is reduced or atherosclerosis is prominent.

This suggests a close link between cardiac function and large vessel atherosclerosis on the one hand and brain perfusion and cognitive functioning on the other. In a national basic and clinical research program supported by the Dutch Heart Foundation, we are testing the hypothesis that impaired hemodynamic status of both heart and brain is an important and potentially reversible cause of vascular cognitive impairment (VCI) offering promising opportunities for treatment. Using a multidisciplinary approach we address the following questions. i) To what extent do hemodynamic changes contribute to VCI?

ii) What are the mechanisms involved? iii) Does improvement of the hemodynamic status lead to improvement of cognitive dysfunction? To this end we have started a clinical multicentre observational study in elderly patients with either clinically manifest VCI, carotid occlusive disease or heart failure and evaluate their cardiac and large vascular function, atherosclerotic load and cerebral perfusion with a comprehensive magnetic resonance imaging (MRI) protocol and thoroughly test their cognitive function. Furthermore epidemiological data from the Rotterdam Study will be gathered to assess the associations between the cardiovascular system and cognitive function in the aging population, while mechanistic studies are being performed in animal studies.

With this approach we have started a national interdisciplinary collaborative network for the study of VCI that will lead to a true multidisciplinary and consensus based approach of the clinical management of VCI, the availability of a diagnostic protocol to assess the hemodynamic contribution to VCI and clarification of the contribution of hemodynamic changes to VCI.

The data from our studies will help to define subcategories VCI patients that may benefit from treatment aimed at improving the hemodynamic status and provide recommendations for future randomized-controlled trials.

Disclosures: The author has nothing to disclose.

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INVITED ABSTRACTS

CARDIOVASCULAR RISK FACTORS AND NEURODEGENERATIVE DISORDERS

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Background: The susceptibility and progression of neurodegenerative disorders may be related to cardiovascular (CV) risk factors, including underlying comorbidities. For example, patients with multiple sclerosis (MS) who reported more than one CV risk factors at the time of diagnosis had an increased chance of ambulatory disability, and the risk increased with the number of CV risk factors reported.

Objectives: To investigate prevalence and association of CV risks with MRI outcomes in neurodegenerative disorders patients. CV risk factors like hypertension, hyperlipidemia and heart disease are associated with increased number of brain white matter (WM) signal abnormalities and decreased gray matter (GM) volume in the general population.

Methods: In a prospective study, 326 relapsing-remitting (RR) and 163 progressive MS (PMS) patients, 61 patients with clinically isolated syndrome (CIS) and 175 age-, sex- and race-matched healthy controls (HCs) were screened for CV risks and scanned on a 3T MRI scanner. Examined CV risks included hypertension, heart disease, smoking, overweight/obesity and type 1 diabetes. MRI measures assessed lesion volumes (LVs) and brain atrophy.

Results: MS patients showed increased prevalence of smoking (51.7% vs 36.5%, $P=0.001$) and hypertension (33.9% vs 24.7%, $P=0.035$) compared to HCs. 49.9% of MS patients and 36% of HCs showed ≥ 2 CV risks ($P=0.003$), while the prevalence of ≥ 3 CV risks was 18.8% in MS and 8.6% in HCs groups ($P=0.002$). In MS patients, hypertension and heart disease were associated with decreased GM and cortical volumes ($P<0.05$), while overweight/obesity was associated with increased T1-LV ($P<0.39$) and smoking with decreased whole brain volume ($P=0.049$). Increased lateral ventricle volume was associated with heart disease ($P=0.029$) in CIS. Having ≥ 2 CV risks was associated with decreased GM and cortical volumes ($P<0.05$) in MS patients.

Conclusions: Patients with neurodegenerative disorders, like MS who present with one or more CV risks showed increased lesion burden and more advanced brain atrophy.

Study conflict: None.

Disclosures: Robert Zivadinov received personal compensation from Teva Neuroscience, Biogen Idec, Novartis, Genzyme, Claret-Medical for speaking and consultant fees. Dr. Zivadinov received financial support for research activities from Biogen Idec, Teva Neuroscience, Novartis, Genzyme and Claret-Medical.

ULTRASOUND CONTRAST IMAGING OF BRAIN HEMODYNAMIC AND PERFUSION

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Studies based on histopathological techniques and on MR imaging demonstrate hypoxia-like brain tissue injury or thrombosis of small veins in patients with Multiple Sclerosis (MS). Applying

dynamic susceptibility contrast Magnetic Resonance Imaging, cerebral mean transit time values were found to be significantly prolonged in MS patients. Recent newly developed ultrasound techniques extend our ability to study the cerebral hemodynamics in patients with neurological disease beyond the conventional blood flow velocity analysis. Different ultrasound methods are currently under investigation that either qualitatively or quantitatively describe brain perfusion. The most widely used technique is bolus kinetics. After applying a ultrasound contrast agent bolus, time intensity curves of the wash-in and wash-out phase of the bolus passage through the brain are registered by imaging at a set frame rate and analyzing the ultrasound intensity in a given region of interest. Based on the time intensity curves, different parameters can be extracted such as peak intensity, time to peak, mean transit time, and incremental time. These parameters can be displayed in a tissue region of interest defined by the examiner. We present the application of contrast enhanced ultrasound (CEUS) to assess *global cerebral circulation time* (CCT) in patients with multiple sclerosis (MS). The method is based on the assumption that the time required by an ultrasound contrast agent to pass from the cerebral arteries to the veins should be prolonged in patients with vessel disorders. Our results suggest that a microvascular or venous outflow impairment could be associated with MS. The CEUS measurement of CCT may be useful tool to disclose cerebral microcirculatory dysfunction in MS patients (Figures 1 and 2).

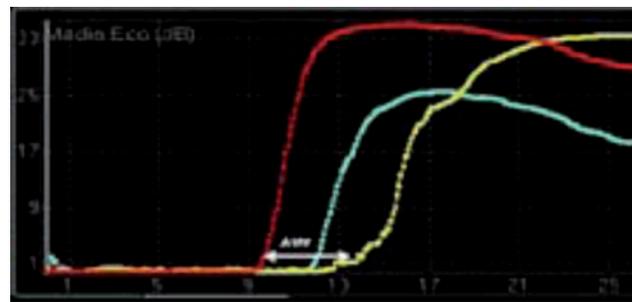


Figure 1. The time-intensity curve analysis displays the acoustic intensity (in dB) during acquisition time in three different region of interest: the carotid artery, thyroid parenchyma without artery/vein, Internal Jugular Vein. The wash-in curves were analysed and three parameters were measured for the ROI: Arrival Time, Time To Peak and Absolute Intensity Peak.

Ultrasound cerebral perfusion imaging is a technique of microvascular imaging that was introduced in the late 1990s. The main clinical focus has been on stroke patients. High MI phase inversion harmonic imaging of the diencephalic plane using the bolus administration of 2.5 mL SonoVueTM (Bracco Imaging) was applied using ultrasound instrument (Philips iU22), equipped with a phased-array transducer (2 MHz). After acquisition (36 to 40 frames), the radiofrequency data were transferred to a PC for further offline analysis. Off-line evaluation comprised region-wise analysis of time-intensity curves (TIC) of predefined ROIs and calculated time-to-peak intensity parameter images. US examinations were performed unilaterally with the transtemporal approach. Standard sonographic brain imaging starts in the axial plane with the probe positioned in the orbitomeatal line.

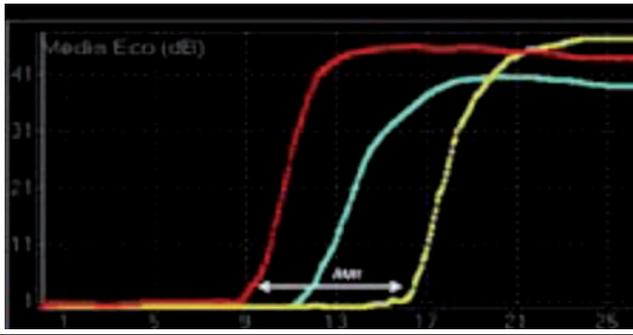
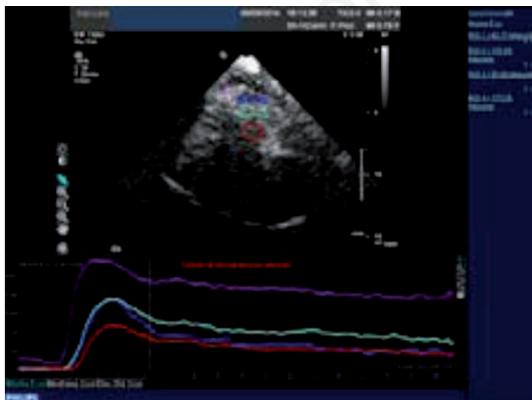


Figure 2. The CCT in a MS patient (bottom) and in a control subject (top). The difference was evident (CCTL in control subject was 3.3 s, in MS patient was 6.9s. The red lined curve depicts the arterial signal, the green lined curve represents tissue signal and yellow lined curve represents the venous signal.

The butterfly-shaped hypoechogenic mesencephalic brainstem appears in the center of the image and serves as an orientation structure. Most brain structures exhibit a low echogenicity. The hypoechogenic mesencephalic brainstem is surrounded by the hyperechogenic basal cisterns. The hyperechogenic aqueduct in the tectum is easily identified. A hyperechogenic midline represents the *brainstem raphe*. By tilting the probe upwards the diencephalic and ventricular plane can be displayed giving view to the third ventricle and the frontal horns of the lateral ventricles as anechogenic zones bordered by hyperechogenic lines where the ultrasound beam meets the ependyma in an orthogonal plane. The basal ganglia are not distinguishable from each other and the white matter because all exhibit a low echogenicity. Visualization of the M2 segment of the middle cerebral artery (MCA) after echo contrast agent injection ensured the correct position in the diencephalic plane. The field of view was set to an imaging depth of 10 cm; the sector angle was 90°. All examinations were performed with the left-sided temporal approach and were digitally recorded and evaluated offline. Regional cerebral echo contrast enhancement was quantified using TIC. Peak intensities (PI), and time to peak intensities (TPIs), and bolus arrival time (AT), were calculated from a model function that was fitted to the measured curve in at least mean square sense. Quantitative data were calculated for the following manually placed ROIs: in the ipsilateral hemisphere, posterior parts of the thalamus, anterior parts of the thalamus, lentiform nucleus, white matter, and MCA (M2 segment) (Figure 3).



Axial B-mode image of the diencephalic scanning plane. Visualization of MCA and parenchymal regions of interest in the ipsilateral hemisphere (posterior parts of the thalamus, lentiform nucleus, white matter). In the lower part of the figure example of the 4 time-intensity curves of the analyzed ROIs. The vertical axis represents the intensity in decibels. The Intensity Peak is higher in the middle cerebral artery, lentiform nucleus territory and white matter than in the thalamus.

Disclosures: The author has nothing to disclose.

TRAUMATIC BRAIN INJURY AND HEMODYNAMIC CHANGES IN THE BRAIN

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One of the most serious health issues facing individuals under the age of 35 is traumatic brain injury (TBI). In the United States alone, it is estimated that 3.5 million individuals sustain a TBI each year, with 275,000 hospital admissions and 52,000 deaths as a result of this disease process. Cerebrovascular pathology is known to play a key role in the morbidity and mortality associated with TBI. Post-mortem evaluations of patients with TBI routinely demonstrate evidence of ischemia. Although the precise nature of TBI-induced ischemia is not entirely known, cerebral vasospasm, hyperemia, global edema, and uncoupling of cerebral blood flow and metabolism have all been observed in patients with this disease process. Also observed is disruption of the blood brain barrier, with concomitant loss of cerebral immune privilege, infiltration of peripheral leukocytes, expression of pro-inflammatory cytokines, and increased production of reactive oxygen species (ROS). The current presentation will review the hemodynamic changes and cerebrovascular pathology that are associated with TBI. These topics will be considered both globally and at the cellular and molecular level to provide insight into the range of cerebrovascular pathology seen in TBI, while examining common underlying mechanisms that may play a role in this disease process. Also considered will be TBI resulting from explosive devices and emerging evidence suggesting particular vulnerability of the cerebral vasculature to this injury mechanism.

Disclosures: The author has nothing to disclose.

IMAGING OF THE MICROVASCULATURE

E.M. Haacke

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Background: The brain's vasculature, as well as perfusion and blood flow, can be probed with and without contrast agents using MRI. Recent evidence shows that vessels as small as 100 μ to 250 μ can be seen with conventional clinically accessible MR angiographic methods in humans and as small as 40 μ in animals.

Objectives: To assess the current state-of-the-art MR imaging methods with and without contrast agents to study the microvasculature of the brain.

Methods: To investigate arterial and venous blood vessels without contrast agent, we review conventional MRA and susceptibility weighted imaging (SWI) methods as well as an interleaved multi-echo version of SWI that includes a short echo MRA. These time-of-flight (TOF) imaging methods have limited SNR and so alternate methods must be sought to improve vessel visualization further. To improve the vessel visibility, two types of contrast agent are evaluated: T1 reducing methods and iron particle T2* and susceptibility based methods such as susceptibility weighted imaging and mapping (SWIM). These are also used to study macromolecular exchange between the venous system and the cerebral spinal fluid (CSF).

Results: With no contrast agents, it is viable to collect 0.5 mm isotropic resolution in a reasonable time period. With a T1 reducing agent, the best resolution to date is 0.25x0.25x0.5 mm allowing vessels as small as 100 μ to 250 μ to be seen. With a T2* iron based contrast agent, in an animal model, the best resolution to date is 42x42x250 μ . Using iron tagged dextran it is possible to see the exchange of the dextran macromolecule across the vessel wall into the veins.

Conclusions: MRA and SWI offer two powerful means to study the neurovascular system.

Key words: MR angiography; susceptibility weighted imaging; cerebral spinal fluid.

Disclosures: Dr. Haacke has a significant financial relationship with MR Innovations, Inc.

IMAGING OF BRAIN MICROVASCULAR DISORDERS: LESSONS FROM THE CADASIL MODEL

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CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is an archetypal ischemic small vessel disease responsible for stroke, dementia and severe disability. The disease is caused by different mutations of the NOTCH3 gene on chromosome 19. CADASIL is considered as a unique model for investigating the classical imaging markers of small vessel disease and for understanding their exact clinical correlates. Imaging studies were previously obtained for determining the natural history of subcortical ischemic lesions, evaluating the cortical consequences of incident lesions, measuring the development of cerebral microstructural and morphological changes. Imaging markers were also recently identified for prognostication and stratification in this model of small vessel disease. Finally, imaging data were found useful for better understanding the pathophysiology of white-matter lesions (so-called *leukoaraiosis*) parallel to studies obtained in the animal model of the disease. The results strongly support that different types of white-matter lesions are present in CADASIL that may be also detected in sporadic small vessel disease.

Disclosures: The author has nothing to disclose.

2D AND 3D ANALYSIS OF VESSELS IN THE RETINA AND THE BRAIN

B. ter Haar Romeny

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Quantitative measurement of geometrical and physiological properties of blood vessels in the retina may indicate early stages of brain and systemic diseases in an efficient and cost-effective way. Retinal vasculature is brain vasculature, and can be imaged easily at high resolution with optical fundus or OCT cameras. Breakdown of the blood-brain barrier, as in diabetes, leads to marked vascular changes, which can be signaled early. This is *e.g.* exploited in large screening programs for diabetes worldwide. We will discuss how typical quantitative imaging biomarkers are measured automatically, as curvature and tortuosity, width, arteriovenous ratio, bifurcation analysis, micro-bleeds, aneurysms and stenosis, angiogenesis, fractal dimension, *etc.* For the enhancement, tracking and segmentation of the tiny vessels we exploit highly robust methods learned from modern insight in brain mechanisms of visual perception. Optical imaging techniques have revealed multi-scale and multi-orientation columns in the visual cortex, which we model mathematically. The micro-vascular analysis can be done in 2D (retina) and 3D (brain, heart). Computer algorithms also enable quantitative analysis and smart interactive 3D visualization of functional imaging, such as 4D blood flow. Flow in larger vessels is still poorly understood. Modern graphics cards (*game cards*) enable cheap and massively parallel renderings. We give examples of modern visualization techniques, inspired by brain connectivity visualization, of 3D/4D flow patterns in brain aneurysms, and aortic arch flow turbulence as an indicator for valve functioning. The message of the presentation is that quantitative analysis of micro-vasculature, and interactive 4D visualization of complex flow parameters in larger vessels is now clinically feasible and accessible.

Disclosures: The author has nothing to disclose.

A NOVEL SONOGRAPHIC METHOD FOR REPRODUCIBLE JUGULAR VEIN PULSE WAVE ASSESSMENT

P. Zamboni, F. Sisini, E. Menegatti, G. Gadda, M. Tessari, M. Gambaccini

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Objectives: We investigated in two phases respectively the feasibility to reliably and non invasively derive the jugular venous pulse (JVP) by means of Ultrasound (US) equipment, and to preliminarily compare JVP in normal people with patients affected by extracranial venous obstructive diseases, typical of the chronic cerebrospinal venous insufficiency (CCSVI).

Methods: Phase 1. Three young healthy subjects underwent B-mode US scan of the internal jugular vein (IJV) in order to acquire a sonograms sequence in the transversal plane. On each acquired sonogram we manually traced the IJV contour and measured the cross sectional area (CSA) as well as perimeter. The CSA dataset represents the US-JVP. The arterial distension wave-form of the subjects were compared with their US jugular diagram. The correlation between the CSA with the perimeter was assessed during the cardiac cycle to verify the IJV distension. For each subject a short sonogram sequence of 4.8 seconds has been recorded. We compared 390 manually traced profiles of the IJV cross sectional area with corresponding values automatically calculated by an algorithm made in house. Phase 2. We blindly compared ten healthy controls with twenty CCSVI patients by the means of the above reported new diagnostic methodology, synchronized with the ECG trace.

Results: Phase 1. For all subjects the US-JVP showed a periodic behaviour. For the three subjects, the Fourier transform showed the pulse duration of the jugular vein. For all the subjects the CSA was found correlated with the perimeter (Pearson coefficient $R > 0.9$) indicating that the IJV in supine position is distended. For all the subjects the mean sensitivity, specificity and diagnostic accuracy resulted around 90%, by comparing the 390 manual tracing with the algorithm. This indicates that JVP can be reliably measured through a rapid analysis of the recording of a real time 5 seconds of sonograms sequence of the IJV. Phase 2. The new methodology to assess the IJV functionality has been compared in a blind pilot study where the JVP was analyzed together the ECG. The analysis clearly shows typical and physiologic curves in the control group respect to abnormalities and high variability assessed in the CCSVI group.

Conclusions: We have shown that a diagram reflecting the JVP can be obtained by analysing an US B-mode movie. Both acquisition and post processing analysis by the means of the developed algorithm require a short time and reduce the operator dependency. Moreover, the significance of the JVP in the CCSVI screening seems promising and warrants a large, blinded, multicenter study.

Disclosures: The authors have nothing to disclose.

FACTORS INFLUENCING AQUEDUCTAL CEREBROSPINAL FLUID MOTION IN HEALTHY INDIVIDUALS

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Background: Increased cerebrospinal fluid (CSF) pulsatility in Aqueduct of Sylvius (AoS) has been associated with various neuropathologies. However, the mechanisms driving the aqueductal CSF (aCSF) pulse are poorly understood.

Objectives: To gain a deeper understanding the factors that influence aCSF motion.

Methods: Twelve healthy young adults (aged 20 to 45 years) with no known neurological disease were investigated using phase contrast MRI. aCSF flow data, together with arterial, venous and CSF flow data at the C2/C3 level, were collected for 32 points throughout the

cardiac cycle (CC). Intracranial fluid volumetric changes were computed from these data to identify the factors that directly influence the aCSF pulse.

Results: The aggregated flow rate signals for all subjects are shown in Figure 1. Mean cervical CSF and aCSF stroke volumes were 801.8 (SD=501.2) and 17.6 (SD=19.3) $\mu\text{L}/\text{beat}$, respectively. Peak negative aCSF flow (towards the fourth ventricle) occurred 14.1% of CC after the arterial peak, while the positive aCSF peak flow occurred after 77.9% of CC (Figure 1). The intracranial venous volume increased by 626.6 μL over the CC, peaking at 64.0% of CC after the arterial peak, while the corresponding change in aCSF volume was 24.0 μL , peaking 71.3% of CC. There was a very strong positive correlation between the intracranial venous blood volume and the aCSF volume ($r=0.966$, $P<0.001$), as illustrated in Figure 2, which shows the change in aCSF volume scaled to match the change in intracranial venous volume.

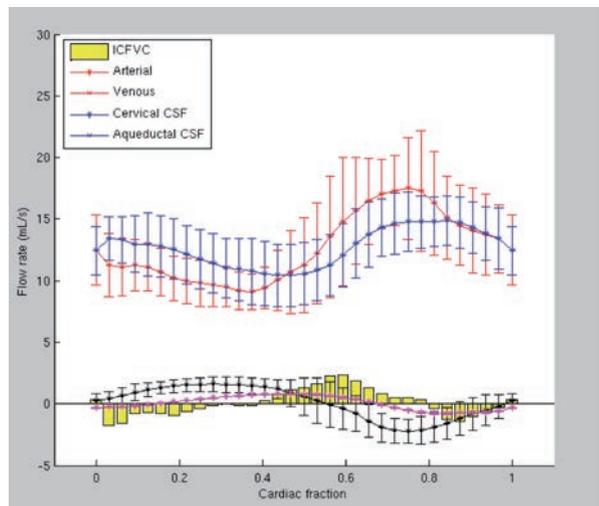


Figure 1. Aggregated fluid flow rates.

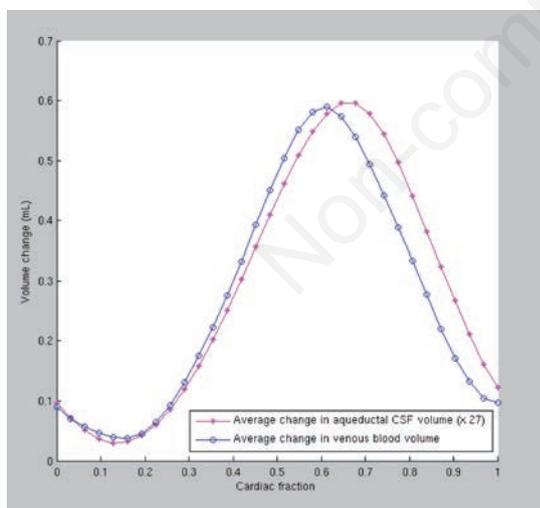


Figure 2. Relative intracranial fluid volumes.

Conclusions: The motion of the CSF in the AoS appears to be strongly influenced by changes in the intracranial venous volume. As the intracranial CSF increases in volume during diastole it causes blood to accumulate in the cortical veins.^{1,2} As the volume of the cortical veins increases, so the volume of the sub-arachnoid space reduces, with the result that CSF is forced up the AoS towards the lateral ventricles. Only when the stored venous blood is voided from the cranium, does CSF flow in the other direction occur in the AoS.

Disclosures: The authors have nothing to disclose.

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UPDATE IN COMPUTATIONAL FLUID MODELING OF THE BRAIN

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Several aspects concur in making the cerebral circulation extremely complex: i) the presence of diffuse anatomical pathways among cerebral vessels (both in the intracranial arterial and extracranial venous circulations); ii) the presence of sophisticated mechanisms which regulate cerebral blood flow following pressure changes and changes in blood gas content; iii) the occurrence of a portion of this circulation within a closed space (the skull and neuroaxis) with a limited volume storage capacity. A deeper understanding of how these complex factors interact reciprocally, and of their possible role in pathological conditions, may be attained with the use of mathematical models and computer simulation techniques. Aim of the presentation is to illustrate the complex mechanisms affecting the cerebral hemodynamics, by making use of computational models developed in past years, and showing some practical examples. The first part of the presentation is focused on the intracranial circulation, laying emphasis on the role of cerebrovascular regulatory mechanisms. A few pathological cases are simulated, to illustrate the complexity of factors operating on brain hemodynamics. An example considers the case of patients with reduced storage capacity and altered CSF circulation (a condition, for instance, typically occurring in patients with severe head injury). In these cases, instability of intracranial dynamics may lead to uncontrollable increase in intracranial pressure, with the development of large ICP waves.¹ A further example simulates hemodynamics in patients with unilateral internal carotid artery stenosis; in this case, local blood flow regulation is progressively lost in the ipsilateral territory with the presence of a steal phenomenon, while the anterior communicating artery plays the major role to redistribute the available blood flow.² The second part presents a very recent extension of this model, in which a detailed description of the extracranial venous pathways (jugular veins, vertebral-azygos vein complex, collateral anastomoses) are included. The model accounts for the changes in jugular vessels lumen occurring when passing from supine to standing, and simulates how these changes can affect flows and pressures in specific points of the system.³ Furthermore, the model provides quantitative predictions on how this redistribution can be altered by stenotic patterns, and how a failure of the extracranial venous drainage may be reflected in the upstream intracranial circulation. We claim these models may have a great perspective value, to help clinicians in reaching a deeper understanding of the multiple mechanisms operating on the brain circulation, and to be acquainted on the complex effects of pathological alterations in brain vessels.

Disclosures: The author has nothing to disclose.

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FLUID DYNAMIC INFLUENCES ON CEREBROVASCULAR ENDOTHELIAL ACTIVATION RESPONSES

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Alterations in blood flow and vascular shear stress are known to induce multiple changes in venous and arterial endothelial cells, including modifications in pro- and anti-inflammatory gene expression, cell differentiation and proliferation, tight junction maintenance, and overall vascular homeostasis. A role for vascular disturbances has also been increasingly apparent in the progression of multiple neurological disorders, such as Multiple Sclerosis and Alzheimer's disease, particularly in initiation and progression of inflammatory processes and potentially blood-brain barrier disturbances. Because changes in vascular shear stress have been implicated in the progression of atherosclerotic disease and in the progression of inflammatory process, we hypothesized that shear stress alterations would lead to inflammatory activation of cerebral endothelial cells. To test this, we exposed human brain endothelial cells (hCMEC-D3) to high or low levels of non-linear shear using microcarrier cultured brain endothelial cells to compare the effects on endothelial activation. We found amyloid precursor protein (APP) was basally expressed in hCMEC-D3 and was released into endothelial microparticles (EMPs) in response to high fluid shear. Similarly, the neurolymphatic marker, lymphatic vascular endothelial hyaluronin acid receptor LYVE-1 was increased in both cells and EMPs in response to high fluid shear. The shear dependent transcription factor Kruppel-like factor 4 KLF-4 was abundant in hCMEC-D3 and appears to increase in response to high and low shear treatment and was transferred into EMPs under both conditions. The tight junction protein Occludin was also increased in hCMEC-D3 in response to both levels of fluid shear, with cleaved forms apparent in sheared MPs. Importantly we found that caveolin-1 was shed into EMPs in response to shear, consistent with these structures as caveolae discharged by cells following exposure to shear.

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VENOUS ABNORMALITIES IN MÉNIÈRE DISEASE

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A brief definition of the Ménière disease, with principal symptoms. Correlations between these symptoms and those usually present in CCSVI affected patients (mainly multiple sclerosis patients). Most evident and frequent results in Ménière disease compared with those with over 2000 CCSVI MS Duplex exams. Anatomic differences and localizations between the two groups of patients at Duplex exams. MRI imaging of MS patients and Ménière disease patients, with comparison and/or differences (anatomical, morphological). Conclusions that mainly highlight the characteristics of the venous abnormalities within Ménière disease.

Disclosures: The authors have nothing to disclose.

ADVANCES IN IDIOPATHIC INTRACRANIAL HYPERTENSION PATHOGENESIS: A FOCUS ON SINUS VENOUS STENOSIS

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Idiopathic Intracranial Hypertension (IIH) is an enigmatic condition characterized by a near daily headache, papilledema, transient visual obscurations, diplopia, vertigo and tinnitus, almost always encountered in overweight women of childbearing age. Symptoms arise from an hypertensive intracranial status which is not associated with any detectable cause. IIH may run without papilledema (IIHWOP) in a part of the patients. IIHWOP may be indistinguishable on clinical basis from primary chronic headache. Available literature evidences suggest that IIHWOP could represent a possible, largely underestimated, risk factor for migraine progression.¹ To date, the presence of sinus venous stenosis at Magnetic Resonance Venography is considered a reliable radiologic marker of IIH.² Sinus stenosis is considered secondary to the raised cerebrospinal fluid (CSF) pressure as it may resolve after CSF withdrawal. However, in recent years the efficacy of endovascular venous stenting in IIH treatment has been consistently reported,³ strongly suggesting that sinus stenosis should be viewed as a causative factor rather than a secondary phenomenon. We propose that in subjects carrying one or more collapsible segments of large cerebral venous collectors, exposed to a number of different promoting factors, sinus venous compression and CSF hypertension may influence each other in a circular way, leading to a new relatively stable venous/CSF pressures balance state at higher values. The mechanism relay on self-limiting venous collapse (SVC) feedback-loop between CSF pressure, that compresses the sinus, and the consequent venous pressure rise, that in turn increases CSF pressure. The result is the *coupled* increase of both pressure values, a phenomenon not expected in presence of sufficiently rigid central veins. Once the maximum stretch of venous wall is reached the loop stabilize at higher venous/CSF pressure values and become self-sustaining, therefore persisting even after the ceasing of the promoting factor. Notably, the SVC is reversible provided an adequate perturbation is carried to whichever side of the loop such as sinus venous stenting, on one hand, and CSF diversion or even a single CSF withdrawal by lumbar puncture (LP), on the other. The SVC model predicts that any condition leading to an increase of either, cerebral venous or CSF pressure may trigger the feedback loop in predisposed individuals. If the SVC might be regarded as a crucial IIH predisposing mechanism, a primary event triggering the CSF and sinus venous higher-pressure balances shift is probably always required. Migraine with and without aura, a disease sharing with IIH a much higher prevalence among women of childbearing age, is associated with waves of significant brain hyperperfusion. These may lead to the congestion of large cerebral venous collectors and could represent a common SVC promoting condition in susceptible individuals and this could account for the high frequency of IIHWOP observed in headache sufferers. The SVC model give reason of the high specificity and sensitivity of sinus stenosis as IIH predictor and of the multiplicity of the factors that have been found associated with IIH. Finally, the SVC model fully explain the enigmatic longstanding remissions that can be commonly observed after a single LP with CSF subtraction in IIH with or without papilledema.

Disclosures: The authors have nothing to disclose.

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ADVANCES IN TREATMENT STRATEGIES OF EXTRACRANIAL VENOUS DISEASE

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Dr. Paolo Zamboni was the first investigator to report the management of internal jugular vein and azygos vein stenotic lesions to

improve symptoms in patients with multiple sclerosis.¹ His original report describes angioplasty of the stenotic lesions using 8 mm and 10 mm angioplasty balloons.¹ Dr. Zamboni called this entity the *chronic cerebrospinal venous insufficiency* or CCSVI.¹ The endovascular management of CCSVI is controversial. The work of some investigators has supported Zamboni's original contribution,²⁻⁶ however, other investigators have not confirmed the encouraging results reported by Zamboni⁷ and for this reason, the concept of CCSVI and its management has been strongly criticized.^{8,9} Endovascular management of jugular vein and azygos vein stenotic lesions has mainly focused on the use of balloon angioplasty^{2,3,10} and certain modifications to the angioplasty technique, including the use of double balloons and cutting balloons have been employed. Measurement of the target vein is imperative; Vein measurement using conventional venography with multiple projections^{2,3} and Intravascular Ultrasound (IVUS) are the most important methods employed for precise vein measurement.^{4,7,11} Endovascular stents have also been used to treat jugular and azygos vein stenoses,⁶ however, reports of complications with the use of endovascular stents have decreased the enthusiasm for their use in these cases.¹² The current presentation will focus on the technical advances in performing endovascular management of CCSVI. Vein measurement and therapeutic methods will be discussed along with the potential advantages and disadvantages.

Disclosures: The author has nothing to disclose.

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VENOUS DYSFUNCTION AND NEURODEGENERATIVE DISEASES

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Several neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease, normal pressure hydrocephalus, etc. have been reported associated with cerebral or/and extracranial venous abnormalities. The present lecture will focus on the current evidences

linking venous abnormalities with AD and cerebral small vessel disease in the elderly, e.g. age-related white matter changes.

Additionally, the relationship between jugular venous reflux (JVR) and multiple neuropsychological performances in patients of AD, results of our latest study, will be presented.

Lastly, a discussion about the postulated mechanisms how venous drainage impairment lead to dysfunctions in AD will be provided.

Disclosures: The author has nothing to disclose.

CLINICAL APPLICATIONS OF VENOUS TREATMENT

M.D. Dake

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Recent data from the literature suggest a greater role of chronic venous insufficiency in the pathogenesis of a variety of brain disorders. The goal of this talk is to review the contributions made in 2014 to our enhanced understanding of the safety and efficacy of the endovascular or open surgical treatment of chronic venous obstruction in patients with a variety of pathologies including multiple sclerosis, transient global amnesia, Alzheimer's disease, Parkinson's disease, postural orthostatic tachycardia syndrome, transient monocular blindness, headaches, and spontaneous intracranial hypertension. Open surgical interventions including, but not limited to operative venous bypass, transposition, venoplasty, and vein interposition have been reported. Endovascular procedures detailed in the medical literature include balloon angioplasty, cutting or scoring balloon angioplasty, self-expanding and balloon expandable stent placement, and stent-grafting. In general, all these therapies have been used to treat stenosis and/or occlusions of the jugular and/or azygous veins associated with increased collateral venous drainage. The relationship between anatomic findings and any symptoms related to the range of neurological disorders listed above has not been established and further research is required.

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ENDOTHELIAL DYSFUNCTION IN NEURODEGENERATIVE DISEASE

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Inflammatory cytokines appear to promote forms of vascular stress in several neurodegenerative diseases and may trigger endothelial disturbances which contribute to blood-brain barrier breakdown and intensification of disease. Using bEnd3 brain endothelial cell model, we found that in response to exposure to TNF- α (20 ng/mL) + Interferon- γ (1000 U/mL) ('T/I') bEnd3 endothelial cells released microparticles from both apical and basolateral domains, (AMPs and BMPs respectively.) Lymphatic vascular endothelial hyaluronic acid receptor (LYVE-1), Prospero homeobox 1 (Prox-1) and vascular endothelial growth factor receptor (VEGFR-3)/Flt-4 have been previously described as *neurolymphatic* biomarkers found in tissue and serum samples in RR Multiple Sclerosis and SP Multiple Sclerosis. These biomarkers, as well as amyloid precursor protein (APP) were also found to be expressed by bEnd3 brain endothelial cells, and were transferred into bEnd3 derived AMPs following T/I-stimulation. The vascular association of these biomarkers in the CNS in distinct clinical forms of MS and experimental neurovascular forms of stress now indicates an endothelial origin for these markers. Interestingly, T/I stimulation also potently induced the transfer of caveolin-1, an important caveolar constituent from bEnd3 brain endothelial cells into AMPs. Similarly, T/I stimulated bEnd3 cells to also release

membrane cholesterol, (measured as BODIPY-cholesterol fluorescence) another important caveolar component, consistent with endothelial microparticles as fluid phase caveolae liberated by cytokine-activated endothelium. By comparison, endothelial nitric oxide synthase (eNOS) was detected within endothelial cells and was decreased by T/I treatment; eNOS also appears to be transferred to AMPs consistent with these particles potentially representing a shed form of circulating eNOS. These findings suggest that neurolymphatic markers induction observed in forms of MS and other of neurodegenerative diseases may represent partitioning of these biomarkers within caveolae which may segregate signaling modules related to neurovascular disease.

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IS THERE A ROLE FOR MAST CELLS DEPENDENT SYNTHESIS OF ENDOTHELIN-1 IN NEURODEGENERATIVE DISEASES?

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Background: In the central nervous system mast cells are found in proximity of neurons and blood vessels. During inflammation, activated mastocytes releases several proteases among which chymase is known to generate the potent vasoactive peptide, Endothelin-1 (ET-1). It is of interest that both mast cell density and ET-1 levels are significantly increased in neurological disorders such as Multiple Sclerosis.

Objectives: To identify the contribution of chymase and ET-1 in a murine model of experimental allergic encephalomyelitis (EAE).

Methods: The ET-1 producing capacity of a mouse chymase isoform Mast Cell Protease 4 (mMCP-4) will be compared to that of its human isoform using a combined recombinant/triple of mass spectrometry approach. In addition, the contribution of systemic mMCP-4 in radiotelemetry instrumented-conscious mice will be assessed. Finally, clinical scores (from 0, normal mouse to 5, moribund state) will be assessed in WT or mMCP-4 KO mice with induced EAE.

Results and Conclusions: The present study demonstrates that both mouse and human chymases are involved in the synthesis of ET-1. Furthermore, preliminary results show reduced morbidity of EAE-induced mice genetically repressed for mMCP-4. We conclude that among several proteases secreted by mast cells in the vicinity of spinal lesions, chymase may play a significant role in the morbid events occurring in the mouse model of Multiple Sclerosis.

Disclosures: Dr. D'Orléans discusses Endothelin 1, big Endothelin-1, Endothelin-1 (1-31), TY 514 69 which is currently unapproved.

ENDOTHELIN-1 AS A POTENTIAL TARGET FOR CHRONIC BRAIN HYPOPERFUSION

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In the brain endothelin-1 (ET-1) is produced and released by endothelial cells lining the blood vessels and by astrocytes. ET-1 exerts its actions through two G-protein coupled receptors subtypes known as ETA and ETB receptors. In basal conditions, the expression of ET-1 in the brain is low, with concentrations of ET-1 in the picomolar range and hardly detectable by immunohistochemical techniques. Significant expression and release of ET-1 by reactive astrocytes occurs in acute CNS injuries, such as ischemic stroke and subarachnoid hemorrhage. It also occurs in a number of neurodegenerative disorders, including Alzheimer's disease, multiple sclerosis (MS), and subcortical vascular dementia (Binswanger's disease), which are

all associated with chronic brain hypoperfusion. In patients with MS we have been able to show a relationship between chronic brain hypoperfusion and increased ET-1 levels. We found that, compared to controls, plasma ET-1 levels in MS subjects were significantly elevated in blood drawn from both the internal jugular vein and a peripheral vein. The jugular vein/peripheral vein ratio was 1.4 in MS subjects *versus* 1.1 in controls, indicating that in MS, ET-1 is released from brain to the cerebral circulation. ET-1 immunohistochemistry on postmortem white matter brain samples suggested that the likely source of ET-1 release were reactive astrocytes in MS plaques. Using arterial spin labeling MRI to noninvasively measure CBF we assessed the effect of the administration of the ET-1A/B receptor antagonist bosentan. CBF was significantly lower in MS subjects than in controls, and increased to control values after bosentan.

Chronic brain hypoperfusion in animal models induces mitochondrial energy failure and oxidative stress. White matter is more susceptible than gray matter, and shows axonal degeneration, apoptosis of oligodendrocytes, myelin breakdown, inflammatory reactions and gliosis. However, chronic cerebral hypoperfusion in rats is also associated with cognitive impairment, and neuronal loss in the hippocampal CA1 region. Axonal degeneration, apoptosis of oligodendrocytes, myelin loss and hippocampal atrophy have been observed in MS, subcortical vascular dementia and Alzheimer's disease. Our finding that reduced CBF in subjects with MS is reversible with an ET-1 antagonist opens the door for exploring new therapeutic approaches for neurodegenerative disorders associated with chronic brain hypoperfusion. ET-1 antagonists are available and are a possible strategy. Another approach consists in targeting the mechanisms leading to enhanced ET-1 expression in reactive astrocytes. In MS there is evidence that ET-1 upregulation in reactive astrocytes may be caused by cytokines that are elevated in MS plaques, including tumor necrosis factor-alpha and interleukin-1b. Targeting these inflammatory pathways might reduce ET-1 expression, restore brain perfusion and slow down disease progression. The underlying mechanisms with regard to Alzheimer's disease and subcortical vascular dementia may be similar, although other mechanisms may be involved.

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CIRCULATING VASOACTIVE FACTORS IN MULTIPLE SCLEROSIS

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In multiple sclerosis (MS) patients, advanced neuroimaging techniques demonstrate cerebral hemodynamic alterations such as chronic cerebral hypoperfusion, prolonged cerebral circulation time and cerebral venous outflow alterations. It is established that MS patients have an impaired sympathetic responsiveness. However, to date, it is still not clear if other vasoactive mediators (alone or in combination) contribute to disease progression and severity. As an example, increased endothelin-1 (ET-1) plasma levels have been demonstrated in MS patients. Other reports document an increase in nitric oxide levels in plasma and cerebrospinal fluid of MS patients. The activity of the NO synthase isoforms (both constitutive-endothelial and inducible/inflammatory ones) is however finely controlled by the endogenous inhibitor asymmetric dimethyl-arginine (ADMA), which is considered a marker of endothelial dysfunction in cardiovascular diseases. In our Scientific Protocol we have studied the modulation of ADMA before and after the endovascular treatment in MS patients. Our data indicates that the levels of vasoactive factors ET-1 and ADMA increase in MS patients respect to control subjects and change in relation to disease severity, cerebral circulation time and endovascular procedures.

Disclosures: The authors have nothing to disclose.

5th Annual Meeting of the International Society for Neurovascular Disease

March 27-29th, 2015 - Naples, Italy

Podium Abstracts

INTERNAL JUGULAR VEIN CROSS-SECTIONAL AREA AND CEREBROSPINAL FLUID PULSATILITY IN THE AQUEDUCT OF SYLVIVUS

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Background: Constricted cerebral venous outflow has been linked with increased aqueductal CSF pulsatility in healthy individuals¹ and MS patients.² However, the relationship between the CSF pulsatility and internal jugular vein (IJV) cross-sectional area (CSA) is unknown.

Objectives: To characterize links between IJV CSA and aqueductal CSF pulsatility in MS patients and healthy subjects.

Methods: 98 relapsing-remitting MS patients (62 males and 36 females; mean age=44.2 years) and 99 healthy controls (48 males and 51 females; mean age=43.9 years) were investigated. CSF flow quantification involved cine phase-contrast MRI, while IJV CSA was calculated using magnetic resonance venography. Cardiovascular risk factor data were collected. Statistical analysis involved correlation, and partial least squares correlation (PLSC), analysis.³

Results: For healthy controls, PLSC revealed a significant relationship ($P=0.001$) between CSF pulsatility and IJV CSA in the lower neck (C5-C7), and a trend for this relationship ($P=0.091$) at C2-C4. PLSC revealed no relationships in MS patients. After controlling for age and cardiovascular risk factors, many significant correlations were identified in the healthy controls between the CSF and IJV variables [e.g. net positive CSF flow and left IJV CSA at: C7-T1 ($r=0.416$, $P=0.002$) and C5-C6 ($r=0.389$, $P=0.003$); and net negative CSF flow and left IJV CSA at: C7-T1 ($r=-0.352$, $P=0.008$) and C5-C6 ($r=-0.349$, $P=0.009$)], whereas there were only two significant correlations in MS patients [i.e. net positive CSF flow and right IJV CSA at: C5-C6 ($r=0.311$, $P=0.035$) and C4 ($r=0.298$, $P=0.047$)].

Conclusions: In healthy adults, higher aqueductal CSF pulsatility is correlated with increased IJV CSA (particularly in the lower neck) in a relationship independent of age and cardiovascular risk factors. This relationship is largely absent in MS patients. Given CSF pulsatility and venous drainage are linked in healthy individuals,¹ it may be that increased IJV CSA is indicative of stasis in venous outflow.

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BLOOD STORAGE WITHIN THE INTRACRANIAL SPACE AND ITS IMPACT ON CEREBROSPINAL FLUID DYNAMICS

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Background: The volumetric changes that occur throughout the cardiac cycle (CC) in the various intracranial vascular compartments are poorly understood. Although blood entering/leaving the cranium is pulsatile, flow in the cerebral vascular bed is non-pulsatile,¹ implying the transient storage of blood.

Objective: To characterise the temporal changes in fluid volume that occur within the cranium throughout the CC.

Methods: Neck MRI data were acquired from 14 healthy adults (age<35), using a 1.5 Tesla scanner. Arterial, venous and cerebrospinal fluid (CSF) flow rate data acquired at the C2/C3 level were standardized to 32 points over the CC. The relative changes in the intracranial arterial, venous and CSF volumes were calculated by: i) integrating the respective flow rate signals to compute the instantaneous volumetric changes (*ivc*); ii) mean centering the respective *ivc* signals; and iii) cumulating the mean centered *ivc* signals to yield the fluid volumetric changes in the cranium throughout the CC.

Results: The aggregated flow rate signals for all subjects are shown in Figure 1, while Figure 2 shows the relative changes in the intracranial arterial, venous and CSF volumes. A strong inverse relationship exists between the arterial and venous volumetric signals ($r=-0.844$, $P<0.001$). As the intracranial arterial blood volume decreases to a minimum during diastole, so blood is stored in the intracranial venous compartments. This coincides with the period when the intracranial CSF volume increases. Only when the intracranial CSF volume peaks and starts to decrease, is the venous blood stored in the cranium allowed to discharge.

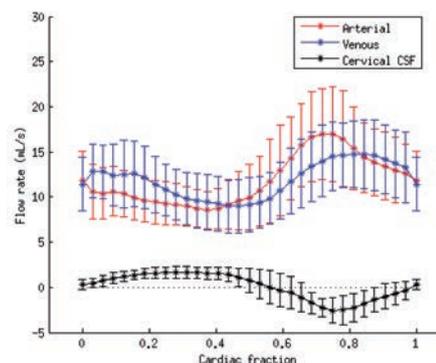


Figure 1. Aggregated fluid flow rates.

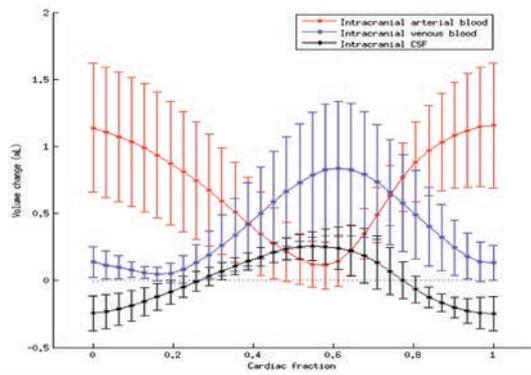


Figure 2. Relative intracranial fluid volumes.

Conclusions: The behavior of the venous pulse is controlled by volumetric changes within the cranium in a process that is mediated by the CSF. This finding supports the hypothesis that CSF interacts with the cortical bridging veins to facilitate the storage of venous blood during diastole.^{2,3}

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CEREBRAL CIRCULATION IN PATIENTS WITH MULTIPLE SCLEROSIS. A COLOR-DOPPLER STUDY OF EXTRACRANIAL ARTERIAL AND VENOUS VESSELS

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Background: Recent studies hypothesized Multiple Sclerosis (MS) to be influenced by alterations of cerebral circulation.

Objectives: To assess whether there is a relation between MS and cerebral circulation, by quantifying arterial inflow and venous outflow and by measuring carotid wall intima-media thickness (IMT).

Methods: 82 MS patients and 53 healthy controls (HC) underwent to extracranial color-Doppler examination in supine and upright for analysis of arterial and venous blood volume flow. Internal Carotid Artery (ICA) was determined 1.5 cm away from the carotid bifurcation. Vertebral artery (VA) was examined in the V2-segment. Cerebral Blood Flow (CBF) was calculated as the sum of flow volumes in both ICA and VA. Mean intima-media thickness (IMT) was measured over a segment of the common carotid artery. Cross-sectional areas of J1, J2 and J3 tracts of IJVs and venous blood flow in the J3 tract of IJV and in the most caudal tract of VV were measured.

Results: The MS group showed lower IJV blood flow than HC in supine position (258.1 mL/m vs 327.7 mL/m; $P=0.025$). No difference was found in the VVs flow. No parameters in the upright position were different. No difference was found in prevalence of IJV stenosis between the two groups. No differences between groups were seen in arterial inflow (CBF MS mean and range: 597.7 mL, 400.2-821 mL, HC 561.7 mL, 242.2-896.7 mL, $P=0.055$) and IMT (MS 0.54 mm, 0.42-0.92 mm, HC 0.49 mm, 0.4-1.09 mm; $P=0.033$).

Conclusions: The results indicate an association between abnormal cerebral venous flow and MS. No differences between MS and HC in CBF and carotid IMT were detected.

Key words: Multiple sclerosis; internal jugular vein; cerebral blood flow; carotid; IMT; echo-color doppler ultrasonography.

Disclosures: the authors have nothing to disclose.

ULTRASOUND-GUIDED SURGICAL PROCEDURE FOR INTERNAL AND EXTERNAL JUGULAR VEINS OCCLUSION IN MICE: PRELIMINARY RESULTS

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Background: The relationship between venous abnormalities and neurological diseases are not widely investigated. Only few studies explored the venous involvement in such diseases. Some studies show that in mice there are multiple connections between intracranial veins and external jugular veins (EJV). Therefore the venous circulation of mouse brain, unlike humans, has two different routes runoff formed by the internal jugular vein (IJV) and EJV. Aim of our study was to develop a mice model of cerebral outflow occlusion in order to assess the correlations between venous stasis and the development of neurological diseases. At this purpose, we used high frequency ultrasound (HFUS) to assess the feasibility of electrocoagulation to obtain neck veins occlusion in mice.

Methods: Fourteen C57/black, female, five weeks old mice were used for this study. 4 mice underwent to bilateral occlusion of the IJV, 4 mice underwent to bilateral occlusion of the EJV, 4 both of the EJV and IJV and 2 mice were used as controls (sham operated mice). All the procedures were performed under general anesthesia with Isoflurane (2%) in 100% oxygen at 0.8 L/min. Blood venous flow of JVs was evaluated before and after surgical procedure by Color Doppler HFUS (Vevo 2100, Visualsonics) with a 40 MHz probe. A ventral midline stab incision was performed on the neck to access the EJV. Deeper blunt dissection was completed, on each side of the trachea, to expose the IJV. An electro-surgical equipment (DIATERMO MB 160, GIMA spa), mounting a small electrode for monopolar coagulation, was used to induce venous occlusion. Skin was closed with 6-0 Vicryl (Johnson&Johnson Medical spa) in a simple continuous pattern and a triple antibiotic ointment was applied over the incision. Sham operated mice were not subjected to electrocoagulation. All procedures were approved by ethical committee and supervised by a Veterinary Doctor.

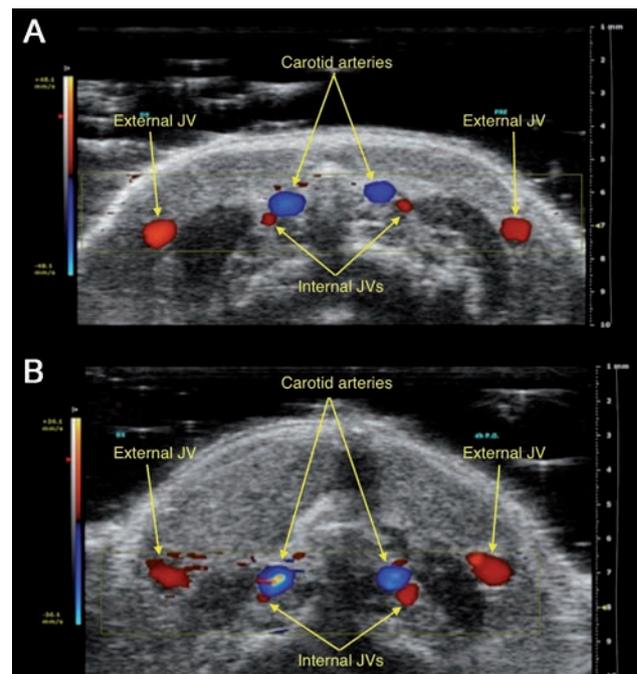


Figure 1. Images of Doppler high frequency ultrasound of neck vessels in normal mice (A) and in sham operated mice (B).

Results: Two of fourteen mice underwent to pulmonary complications during the surgical procedure, therefore the mortality was of 14%. The IJV and EJV were well identified with color Doppler HFUS prior (Figure 1A) and after the surgical procedure (Figure 1B). In all cases examined, HFUS allowed us to confirm the absence of flow in the obstructed veins after the electrocoagulation procedure. All survivors are under neurological examination to assess the brain damage secondary to neck veins occlusions.

Conclusions: In our study, we evaluated the feasibility of ultrasound-guided surgical procedure that resulted a procedure with low mortality and efficacy in 100% of survivors. As the neck mouse veins anatomy is not similar to human, *in vivo* imaging of normal neck vessels is necessary for the evaluation of animal models. Further studies are in progress to evaluate brain damage secondary to the occlusion of extracranial veins in mice. See shadow back due to surgical suture (B).

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MULTIPARAMETRIC AUTOMATED SEGMENTATION OF BRAIN VEINS

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Background: Manual segmentation of brain vessels in a typical MR dataset is both complex and time-consuming; therefore automated approaches are actively sought for, as they also improve the reproducibility of the results.

Objectives: To present a multiparametric segmentation method (MPS) that, starting from a vessel likeliness function (Vesselness) and R2* map of the brain, applies an Expectation Maximization (EM) algorithm to the bivariate distribution of the data to classify each voxel as belonging or not to veins.

Methods: Based on the assumption that a voxel belonging to a vein has high Vesselness and R2* values, on the log-scale joint histogram of the maps, the voxels whose Vesselness is higher than 0 were assigned to 3 main classes: i) a Gaussian distribution with low R2* and Vesselness (false positives enhanced by Vesselness); ii) a class with R2* value above a given threshold; iii) another Gaussian distribution with medium-high value of R2* and high value of Vesselness, the last two truly corresponding to veins. Through an EM algorithm, the parameters of the 3 classes were estimated and the voxels belonging to the 2 vessel classes were identified. The performance of the MPS was compared to the Vesselness thresholding (VT) by blindly grading on a 0-5 scale the accuracy of vascular tree depiction.

Results: The semiquantitative analysis clearly showed that MPS achieved greater accuracy in vessel display (scores 4-5 in 88% of the test-sample) than VT (scores 2-3 in 74% of the test-sample). In particular, false positives were the main pitfall of VT compared to MPS.

Conclusions: Combining the information obtained from Vesselness and R2* maps, the MPS substantially increased sensitivity and specificity of the monoparametric thresholding based on vesselness images only.

Key words: Brain veins; vessel enhancing diffusion; R2* map; expectation maximization algorithm; multiparametric segmentation.

Disclosures: The authors have nothing to disclose.

DISTURBED INTRACRANIAL VENOUS HAEMODYNAMICS AND MACROMOLECULE TRANSPORT ACROSS VESSEL WALLS: A MATHEMATICAL MODEL

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Background: The recent association of extracranial venous strictures to Multiple Sclerosis¹ has posed a number of partly unresolved hypothesis, one of them being intracranial disturbed flow and venous hypertension. By means of a global mathematical model for the human circulation² it has been found that intracranial flow disturbances and venous hypertension are possible. Another step in the chain of events leading to MS, involves increased permeability of the BBB due to altered venous haemodynamics and potential transport of colloids from the vessel lumen to the brain tissue. It is desirable to construct a mathematical model that addresses this issue; preliminary results are given in.³

Objectives: To describe a simple mathematical model for plasma and molecule transport across blood vessel walls and perform a parametric study to identify biophysical quantities that affect vessel wall permeability and transport.

Methods: We use a mathematical model to study the consequences of brain venous hypertension regarding macromolecule transport across vessel walls.

Results: We studied the effect of three parameters: i) glycocalyx degradation; ii) local hydrostatic pressure; and iii) increase in pore number and/or radius. Our results show that an increase in each of these three parameters results in increased plasma filtration and/or solute extravasation, as one would have expected.

Discussion and Conclusions: Mathematical modelling is helping in elucidating recently proposed medical hypotheses based on the empirical observation of a strong association between MS and extracranial venous strictures. Computational quantification supports the plausibility of the proposed chain of events: extracranial venous strictures, disturbed intracranial venous flow, venous hypertension, increased plasma filtration and/or solute extravasation. More research is needed.

Disclosures: The authors have nothing to disclose.

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POSTER ABSTRACTS

VITAMIN K CREAM REDUCES CUTANEOUS REACTIONS TO INTERFERON β 1a INCLUDING ERYTHEMA: THE MULTIPLE SCLEROSIS EXPERIENCE

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Background: Injectable drugs are usually associated with adverse effects leading to poor adherence and incomplete efficacy. Interferon beta (IFN β) is an approved injectable drug for multiple sclerosis but it can cause a variety of local and systemic adverse events (AE), which include injection site pain, burning and erythema together with itching that can persist for several days, probably because of increased local release of histamine. Topic vitamin K seems to be useful to prevent, or at least to reduce, the development of burning sensations acting as cofactor for the γ -glutamyl-carboxylase, taking part in a reaction involved in calcium binding and, as a consequence, in the interaction between coagulation factors and phospholipid layers. The mechanism of vitamin K in improving the cutaneous redness is probably local but not yet fully understood.¹⁻⁴

Objectives: To evaluate if a vitamin K cream local application could reduce injection-site reactions in MS patients treated with subcutaneous IFN β .

Methods: This is a prospective, crossover interventional study. We enrolled RR MS patients treated with subcutaneous IFN β 1-a with injection-site reactions. Patients were randomly assigned to receive Vitamin K cream from baseline or not (with a ratio of 1:1). At week 8 crossover took place. Visual Analogic Scale (VAS) for burning and pain and measure of the maximum width of erythema was performed at 0, 4, 8, 12 and 16 week. Linear mixed model was assessed to evaluate the variability of continuous parameters (*i.e.* VAS or erythema width) over time in relation to vitamin K cream use considering repeated measures. A P value <0.05 was considered statistically significant.

Results: We enrolled 123 subjects. At baseline median erythema width was 30 mm, VAS median score for burning sensations was 40 and for pain was 47. Vitamin K cream led to a significant reduction of 3.4 mm (P<0.001; CI 95% -5.3; -1.6) of the erythema width in vitamin K treatment period with respect to the period without treatment. Vitamin K cream led also to a significant reduction of 3.5 points (P=0.014) of burning VAS score and 4.3 points (P=0.002) of pain VAS score.

Conclusions: Vitamin K cream could be a helpful tool to improve treatment adherence for injectable drugs in MS. It is effective in reducing erythema, burning and pain sensation over the injection site. The mechanism of vitamin K in improving the cutaneous redness is not completely understood but probably it could take part in some reactions involved in calcium binding and, as a consequence, in the interaction between coagulation factors and phospholipid layers.

Disclosures: The authors have nothing to disclose.

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EXTRACRANIAL VENOUS ANOMALIES, INTRACRANIAL HYPERTENSION, MS AND IPD: A MATHEMATICAL AND MRI STUDY

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Background: Recent evidence has suggested that the venous system plays a role in several neurodegenerative pathologies. The challenges lay with the complexity of the venous network in the brain and the difficulty to measure pressure in the brain veins.

Objectives: To assess the impact of unilateral stenoses in the internal jugular veins (IJVs) on pressure changes in the brain, by combining patient-specific MRI flow data and a mathematical model, focusing on possible correlations with MS and IPD.

Methods: A global computational hemodynamic model for the human circulation was utilized. 2D TOF and 3D contrast-enhanced MR venography of the head and neck of a healthy subject were collected. Two sets of simulations for stenotic veins were performed, one for the LIJV and one for the RIJV for this left dominant individual. The stenosis was induced by reducing the lumen of the respective valve to 0.01%.

Results: For the LIJV stenosis, significant pressure changes occurred in the SSS (+1.6 mmHg, +21%), internal cerebral veins and the basal vein of Rosenthal (1.5 mmHg, 11%). Changes at the C2/C3 level and in the pterygoid plexus also occurred. Negligible changes in the arterial system were observed. For the RIJV stenosis, changes in the flow in other veins were now less evident, although some modifications were seen in the straight and transverse sinuses.

Conclusions: Significant changes in pressure inside the brain occurred when the LIJV was altered, especially in the midbrain and basal ganglia draining veins, where iron build up over time is observed in MS and IPD patients. We also observed pressure changes in veins draining the eyes. These can lead to ophthalmic problems, which have been related to MS. These results agree with the recent correlation found between unilateral venous abnormalities, MS and IPD.

Key words: Intracranial hypertension; MS; IPD; MRI; mathematical modeling.

Disclosures: The authors have nothing to disclose.

HEMODYNAMIC MODEL FOR THE STUDY OF CEREBRAL VENOUS OUTFLOW: COMPARISON WITH EXPERIMENTAL RESULTS

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Background: Blood flow redistributions and pressure variations due to posture changes in patients affected by vascular diseases are associated with the onset of venous obstructions. A hemodynamic model for the study of cerebral venous outflow was developed to study the correlations between extracranial blood redistributions and changes in the intracranial environment.

Objectives: To validate the model outcomes using flow data from a large cohort of stenotic and non-stenotic people obtained with magnetic resonance (MR) techniques.

Methods: The model results were tested using a MR flow dataset of 690 supine people (stenotic/non-stenotic ratio=372/318, multiple sclerosis/healthy controls ratio=571/119). Internal jugular veins (IJVs) showing a cross section area (CSA) of less than 25 mm² at the lower half of the IJV body was considered stenotic, while a CSA of less than 12.5 mm² was considered stenotic for the upper IJV body. Phase-Contrast MR images at the C2/C3 and C5/C6 spinal cord level were used to quantify blood flow.

Results: Model simulations of the fraction of cerebral blood flow drained by the jugular ducts for supine nonstenotic people are in agreement with MR data (0.93 and 0.82, respectively), as well as the flow in the spinal ducts (0.06 and 0.09), both with a statistically significant P-value. The same simulations agree with measurements of lack of jugular drainage and increase of extrajugular drainage due to different stenotic patterns. Moreover, there is agreement with upright blood flow data assessed by Echo Colour Doppler methodology.

Conclusions: The present model correlates vascular diseases, extracranial blood redistributions and changes in the intracranial environment, taking into account the posture variation and the amount of blood coming from anastomotic connections and extrajugular drainage pathways.

Key words: Mathematical modeling; cerebral drainage pathways; posture dependence; ultrasound and magnetic resonance flow quantification.

Disclosures: The authors have nothing to disclose.

IMPACT OF EXTRACRANIAL VENOUS OUTFLOW DISTURBANCES ON PETROSAL SINUSES PRESSURE IN SUDDEN SENSORINEURAL HEARING LOSS: A COMPUTATIONAL PILOT STUDY

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Background: Anecdotal reports of extracranial venous outflow disturbances have recently been linked to sensorineural hearing loss (*i.e.* Ménière disease). To date, direct measurements of venous hypertension in the main intracranial route of drainage of the inner ear through invasive methods are unavailable. As an alternative, the use of a computational model makes possible cerebral haemodynamical quantifications. Extracranial venous outflow and post analysis was blindly assessed in healthy control (HC) and in a group of four patients with different outcome of sudden sensorineural hearing loss (SSNHL).

Objectives: To study the impact of extracranial cerebral venous outflow on bilateral pressure of the superior and inferior petrosal sinuses

(SPS, IPS), posterior auricular, deep facial, mastoid emissary, internal jugular veins.

Methods: Making use of a global, mathematical model for the human circulation (previously validated against *in vivo* MRI data), we performed five sets of simulations for subjects in supine position, by considering different outflow anomalies. Simulations were realized after quantifying flow anomalies eventually found by the means of a validated echocolorDoppler quantification protocol. Finally, results were compared with the clinical outcome.

Results: The main finding was the significant increased pressure calculated in the right SPS and inferior petrosus sinus in patients with blocked outflow and collateralization at the level of the right IJV obstructed valve. This finding seems to be relevant for the outcome of the patients since 2 patients with such haemodynamic pattern did not show any threshold recovery. To the contrary the patient with not significant raising pressure in the petrosus sinuses responded to treatment.

Conclusions: The mathematical model applied to our validated ECD protocol of outflow quantification seems to provide coherent and unconventional clinical information on the drainage of the inner ear. This innovative approach was proven to be feasible by the present pilot investigation and warrants further studies with an increased sample of patients.

Key words: Cerebral venous haemodynamics; petrosus sinus hypertension; mathematical modeling; quantification of venous outflow; echocolorDoppler; sudden sensorineural hearing loss (SSNHL).

Disclosures: The authors have nothing to disclose.

ENHANCED VESSELNESS MAPPING TO DETECT SMALL CEREBRAL VEINS ON SWI IMAGES

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Background: Cerebral veins are visualized by Susceptibility Weighted Imaging (SWI), which may highlight vascular abnormalities in different cerebral diseases. Assessing the vascular anatomy in a 3D computer model by a vascular extraction algorithm may improve the study of structural and functional abnormalities in vascular diseases.

Objectives: To implement a modified version of Vessel Enhancing Diffusion (VED) filter and test its application to SWI datasets at different flip angles.

Methods: A multi-scale (0.1 to 1 mm) vessel enhancement filter was applied to several 3D SWI datasets acquired by a 3T scanner (FAs=[3~20]°, TR=31 ms, TE=22.14 ms, voxel size=0.5x0.5x1 mm³). For each scale and voxel the Hessian tensor was calculated and a vesselness estimate was computed on the basis of the Hessian eigenvalues, to distinguish tubular from non-tubular structures. The voxel-by-voxel maximum of these estimates was evolved according to a scheme of anisotropic diffusion highly restricted when perpendicular to tubular structures (VED). To improve the VED filtering and obtain high-SNR continuous 3D model of the veins, the diffusion time was set to 0.2, the sensitivity *s* to 3 and, at each diffusion step, the vesselness function was thresholded, suppressing all values below 0.02.

Results: The visual inspection of the vesselness maps obtained varying the SWI flip angle suggests that the better compromise between sensitivity to vessels and specificity against CSF-filled sulci was reached using flip angles close to the Ernst angle of gray matter (~12° for the given TR).

Conclusions: Dynamical thresholding of the vesselness function within the diffusion evolution provides an increased specificity in vessel visualization that, combined with a proper choice of the acquisition flip angle, allows the detection of deep medullary veins barely visible on the original SWI.

Key words: Susceptibility weighted imaging; cerebral vein; vessel enhancing diffusion; vesselness function.

Disclosures: The authors have nothing to disclose.

VENOUS THEORY OF MS AND OTHER NEUROLOGICAL DISEASE

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Background: The aim of this study was to answer the question whether chronic cerebrospinal venous insufficiency (CCSVI) is a specific syndrome only in MS or it is found in other neurological diseases.

Methods: The research included 1066 patients examined for chronic cerebrospinal venous insufficiency (CCSVI): MS - 1000, ALS - 12, Parkinson - 17, and Alzheimer - 9, CVST - syndrome transitory global amnesia - 2, STGA - cerebral venous sinus thrombosis - 2, migraine - 24. The CCSVI and neurological diagnoses were established clinically, with Echo-Doppler, phlebography, MRI, CT and EMG. Endovascular therapy of CCSVI - dilatation or stenting of the jugular veins was performed.

Results: CCSVI was established in 94% of patients with neurological diseases. We found CCSVI in 96 % of MS patients and 77% in other neurological diseases. Endovascular therapy was performed in all patients with CCSVI: venous dilation and/or stenting of the venous stenosis of jugular and azygos vein. After therapy reported clinical effects: 61% of the patients had positive clinical effects, 65% had increase in QOL.

Conclusions: CCSVI was established not only in patients with MS, but in patient with other neurological diseases. Based on these studies, we believe that a vein theory would explain the presence of CCSVI in various neurological diseases. This is the most likely hypothesis. According to venous theory, CCSVI is a key factor in the development of neurodegenerative, autoimmune and other neurological disease. The improved vein drainage after endovascular therapy of CCSVI had very good clinical effect with low number of post-procedure complications. It is necessary to make the randomized trials.

Key words: CCSVI; MS; ALS; Parkinson; Alzheimer; CVST; STGI.

Disclosures: The authors have nothing to disclose.

CCSVI IN MÉNIÈRE'S DISEASE: DIAGNOSIS AND TREATMENT

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Objectives: To evaluate by the means of Doppler ultrasound and phlebography the relationship between Ménière's disease and chronic cerebrospinal venous insufficiency (CCSVI) and to test whether angioplasty is an effective procedure in improving symptoms.

Methods: i) Phase 1: 150 patients diagnosed with definite Ménière's disease (AAO 1995) who had gained no benefit by medical therapy, underwent echo-enhanced color Doppler sonography using the Zamboni protocol to check for CCSVI. One-hundred (100) healthy subjects matched for age and gender acted as controls. ii) Phase 2. In 40 of ECD positive Ménière's cases we performed a venogram and the diagnosis of associated CCSVI was confirmed. These patients were treated by angioplasty of the Internal Jugular Vein, then re-tested respect the baseline scales of Ménière's disease. Twenty of them had a 18-month follow-up.

Results: Out of a total of 150 patients with Ménière's disease, an ultrasound diagnosis of CCSVI was made in 135 patients (90%). In the healthy population, was found in only 10% of cases. In fourthy patients venography confirmed the CCSVI diagnosis and percuta-

neous transluminal angioplasty (PTA) proved to be effective in 80% of patients, with significant improvement of several scales of audiological and vestibular function at 18 month follow-up.

Conclusions: The prevalence of CCSVI in patients with Ménière's disease is higher than in healthy subjects; PTA seems useful because of an improvement in symptoms with audiological and vestibular functions better in the majority of patients.

Disclosures: The authors have nothing to disclose.

ULTRASOUND B-MODE TO ASSESS THE JUGULAR VENOUS PULSE

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Objectives: Poor functionality of the brain drainage can lead to brain problems such as delaying venous return and as reported by Zivadinov and Chung, *Mounting evidence suggests that a number of inflammatory and neurodegenerative central nervous system disorders may be related to vascular factors*. Since internal jugular vein (IJV) is considered to be the main route for the drainage of the brain when the body is in supine position various authors have investigated the possible relationship between abnormal conditions of the jugular vein functionality and neurological disorders. As pointed out by Zivadinov, precise assessment of the cerebral venous return and hence of the IJV functionality is needed in order to relate it with such neurological disorders. Unfortunately, the proper ultrasound Doppler assessment of the IJV blood ow is challenging because the difficult to assess accurately the blood velocity needed for the ow calculation. In fact, IJV CSA varies along the vessel cervical course and also change in time because of its pulsation. For this reason we are investigating alternative approaches to assess IJV drainage functionality based on B-mode modality. We believe that jugular venous pulse (JVP) waveform can be used to investigate IJV drainage functionality. In the past, already MacKay, used the JVP obtained using a polygraph to assess the change in venous return induced by posture changing. B-Mode ultrasound technique allows the cross section of the IJV to be easily displayed, and therefore the area and perimeter variation to be measured along the cardiac cycle. Our idea is that it is possible to obtain the JVP using a sequence of sonograms of the IJV obtained in B-mode. The idea is to create a diagram of IJV CSA respect the time; in fact when the IJV is distended (not collapsed), its transmural pressure (*i.e.* internal minus external pressure) and its CSA are correlated and therefore the time diagram of the CSA reects the JVP. In this preliminary study, we explore the possibility to produce a diagram reecting the JVP CSA variations by means of real time B-Mode ultrasound sequences. Such approach has been already used to dynamically investigate the arterial distension waveform (ADW) of 2 the carotid arteries but it has not been used to assess the JVP.

Methods: Three young healthy subjects underwent B-mode US scan of the internal jugular vein (IJV) in order to acquire a sonograms sequence in the transverse plane. On each acquired sonogram the IJV contour was manually traced and both cross sectional area (CSA) and perimeter were measured. For every acquired sequence both the measured CSA and the acquisition time of the sonogram were also collected. The CSA data set represents the USjugular diagram (USJD). The precision of the operator was evaluated. The US jugular diagrams were then produced by an algorithm developed in house. The sensitivity (SE), specificity (SP) and accuracy (AC) of the algorithm has been evaluated. Discrete Fourier transform and auto-correlation function of the jugular diagrams were evaluated to assess their periodicity. The arterial distension waveform of the subjects was compared with its USJD. The correlation between the CSA and the perimeter was assessed during the cardiac cycle to verify the IJV distension. This study was in

accordance with the Ethical Standards of the Committee on Human Experimentation of the Azienda Ospedaliera Universitaria di Ferrara, Italy.

Results and Discussion: For each subject a short sonogram sequence of few seconds was recorded and the obtained USJD showed a periodic behavior. The coefficient of variation of the manual US jugular diagram measurement resulted around 0:015. For the three subjects, the Fourier transform showed the pulse duration of 3 the jugular vein. We compared 390 manually traced profiles of the IJV cross sectional area with corresponding values automatically calculated by an algorithm made in house. For all the subjects the accuracy resulted over 90%. Besides, for all subjects the CSA was found correlated with the perimeter (Pearson coefficient $R > 0.9$) indicating that the IJV in supine position is distended and then the Young modulus for the IJV can in principle be obtained by the measurement of the pulse wave velocity.

Conclusions: We have shown that a diagram reflecting the JVP can be obtained by analyzing an US B-mode sonogram sequence of the IJV; such diagram can result in a new methodology to assess the IJV functionality.

Key words: Internal jugular vein; jugular venous pulse; edge detection; venous return; cerebral outflow.

Disclosures: The authors have nothing to disclose.

EVALUATION OF CLINICAL CONDITION AFTER PTA OF JUGULAR AND AZYGOS VEINS IN 815 PTS AFFECTED BY MULTIPLE SCLEROSIS

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Since the physical disability in MS (multiple sclerosis) disease is of great importance, therefore Q of L (quality of life) measurements have been considered increasingly important with regards to evaluating disease progression, treatment and management for care to MS patients. In all our patients we investigated two symptoms: i) Fatigue; ii) Bladder conditions. We examined 815 consecutive patients after PTA (percutaneous transluminal angioplasty) of jugular and azygos veins, starting from October 2010 to July 2014. The evaluation has been done from 2 to 42 months after PTA. The sample in our study showed a large variability in EDSS score (expanded disability status score, ranging from 1.5 to 7.5) and thus represented the physical performance of the MS population to a great extent. The three principal types of MS were enrolled: RR 522 patients 65%; SP 229 patients 28%; PP 54 patients 6.6%. 10 patients were not enrolled because of uncertain classification. Age from 18 to 73 - average 43 (F 540 M 285; ratio 2-1). The 2 symptoms, fatigue and conditions of the bladder, were present in a very evident way. The meaning of the FATIGUE is a subjective deep lack of physical and mental energy perceived from the patient even in rest conditions. From the fatigue we used the scale of analogic evaluation (VAS), where the patient is able to refer a value from 0 to 10 about personal fatigue. BLADDER: the necessity to empty the bladder in the morning from almost every hour before PTA, and roughly 4 to 6 times after PTA; at night time, the necessity was from 1-4 times prior to PTA, to 0-1 after PTA. In the 85% the pts are in hurry with the impossibility to wait; in 15% there was the difficulty to empty the bladder. The results about these two items, very important for Q of L, has been a complete resolution of the fatigue and normalized bladder in 458 pts (60.4%). We excluded in the investigation patients with moderate improvement of the 2 items. We would like to highlight that, among the three types of MS in the 815 pts, it was more difficult to obtain an evident disappearance of the symptoms in SP (secondary progressive) and PP (primary progressive) MS types. We would like to underline also our diagnostic approach with MS patients: the examination is carried out with echocolor Doppler in the haemodynamic ward before, during and at the end of PTA procedure.

Disclosures: The authors have nothing to disclose.

CIRCULATING PROFILE OF ENDOTHELIAL DYSFUNCTION AND COAGULATION/INFLAMMATION ACTIVATION IN PATIENTS WITH MULTIPLE SCLEROSIS AFTER ENDOVASCULAR TREATMENT OF CHRONIC CEREBRO SPINAL VENOUS INSUFFICIENCY:

A PROSPECTIVE STUDY

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Background: The blood brain barrier (BBB) is a multi-cellular complex establishing a stable and immunologically privileged environment for neural functions. Recently, changes in cytokine, metabolic and growth modulating networks between BBB endothelium and support cells have been thought to contribute to vascular injury in Multiple Sclerosis (MS).

Objectives: We performed a monocentric observational prospective study to evaluate coagulation activation, endothelial dysfunction parameters and circulating cytokines in patients with MS undergoing endovascular treatment for cerebro-spinal-venous insufficiency.

Methods: Between February 2011 and July 2012, 144 endovascular procedures in 110 patients with MS and *chronical cerebro-spinal venous insufficiency (CCSVI)* were performed and they were prospectively analyzed. Each patient was included in the study according to previously published criteria, assessed by the investigators before enrollment.

Results: Endothelial dysfunction and coagulation activation parameters were determined before the procedure and during follow-up at 1, 3, 6, 9, 12, 15 and 18 months after treatment, respectively. After the procedure, patients were treated with standard therapies, with the addition of mesoglycan (50 mg twice-day). Fifty-five percent patients experienced a favorable outcome of MS within 1 month after treatment, 25% regressed in the following 3 months, 24.9% did not experience any benefit. No major complications were observed. Coagulation activation (activated FX and F1+2), endothelial dysfunction parameters (PAI-1, t-PA, D-Dimers) and cytokines (sICAM, sVCAM, IL-1 and IL-6) were shown to be reduced at 1 month and stable up to 12-month follow-up, and they were furthermore associated with a good clinical outcome.

Conclusions: Endovascular procedures performed by a qualified staff are well tolerated. Correlations between inflammation, coagulation activation and neurodegenerative disorders here demonstrate that hemodynamic correction is able to restore the normal levels of several coagulation/inflammatory/angiogenic factors characterizing CCSVI in MS.

Key words: CCSVI; coagulation activation; endothelial dysfunction.

Disclosures: The authors have nothing to disclose.

CORTICAL SOURCES OF RESTING STATE EEG RHYTHMS DIFFER IN RELAPSING-REMITTING AND SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS

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Background: Multiple sclerosis (MS) is one of the most common causes of neurological disability in adults with an unpredictable clinical course and variable manifestation. There are two major forms of MS, namely relapsing-remitting (RR) and secondary pro-

gressive (SP). It was observed that resting state electroencephalographic (EEG) rhythms are abnormal in MS patients, but it is unclear if they can reflect different neurophysiologic abnormalities in RR and SP forms.

Objectives: Here we tested the hypothesis that abnormal cortical sources of resting state EEG rhythms distinguish RR and SP at group level.

Methods: Resting state eyes-closed EEG activity was recorded in 43 RR, 26 SP, and 60 matched healthy subjects. EEG rhythms of interest were δ (2-4 Hz), τ (4-8 Hz), α 1 (8-10.5 Hz), α 2 (10.5-13 Hz), β 1 (13-20 Hz), and β 2 (20-30 Hz). LORETA freeware estimated cortical EEG sources for statistical comparison between the two groups.

Results: Compared to the control group, the MS sub-groups showed an amplitude decrease of widespread α 1 cortical sources and an amplitude increase of parietal delta cortical sources. Furthermore, frontal and temporal delta sources were higher in amplitude in the RR compared to the SP sub-group.

Conclusions: The present results suggest that cortical sources of resting state low-frequency EEG rhythms differ in two common phenotypes of MS patients such as RR and SP. These findings motivate the use of the present EEG biomarkers for future investigations on the effect of standard and new interventions (*i.e.* medications, rehabilitation, cerebrovascular, *etc.*) in RR and SP patients.

Key words: Multiple sclerosis; relapsing-remitting; secondary progressive; electroencephalography; low-resolution brain electromagnetic tomography.

Disclosures: The authors have nothing to disclose.

PERCUTANEOUS TRASLUMINAL ANGIOPLASTY OF AZYGOS VEIN IN PATIENTS WITH MULTIPLE SCLEROSIS AND CHRONIC CEREBRO SPINAL VENOUS INSUFFICIENCY. A SINGLE CENTER EXPERIENCE

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Background: Chronic cerebrospinal venous insufficiency (CCSVI) is a recently discovered syndrome mainly due to stenoses of internal jugular (IJV) and/or azygos veins (AZ). The aim of the present study is to retrospectively evaluate technical success after PTA±stenting in a cohort of patients with multiple sclerosis (MS) and CCSVI.

Methods: From September 2010 to October 2014 a total of 2435 MS patients (1391 females) underwent selective venography from a left common femoral vein access, followed by balloon angioplasty±stenting at the same session. All the patients had previously been evaluated for CCSVI with Color Doppler Ultrasound at different Institutes. Left common iliac, ascending lumbar, vertebral and internal jugular veins as well as azygos territory were selectively studied in all cases. Interventional treatment was performed whenever achievement of an improved flow through the AZ was deemed possible. Endovascular treatment was carried out as an outpatient procedure in all patients.

Results: Selective venography of the AZ was performed in 2433 patients. Two patients showed no evidence of AZ vein despite several attempts at finding it. Percutaneous transluminal angioplasty±stenting of the affected AZ was performed in 2119 (87.1%) patients. Balloon angioplasty alone was performed in 2095 cases (98.9%) whereas additional stent placement was required in 24 patients (1.1%). The decision to implant a stent was taken following 3 unsuccessful attempts at dilating the vein (23 cases) or following a vein rupture occurring at the time of balloon dilatation (1 case). In all 23 patients with unsuccessful AZ dilatation a severe kinking of the vessel was noted at confirmation angiography. Balloon angioplasty alone showed improvement of the venous drainage >30% in 1849 out of 2119 (87.2%) whereas stenting proved to be successful in 21 out of 23 patients (91.3%). Major complications included one (0.05%) surgical opening of common femoral vein to remove balloon fragments and one (0.05%) AZ rupture requiring hospitalization. Minor complica-

tions included, 3 (0.15%) procedure-related technical issues, 5 (0.24%) transient atrial fibrillation requiring a further 12-hour hospital stay, 15 (0.7%) slight bleeding or haematomas in the groin (3 requiring further hospital care the day after intervention and 5 prolonged hospital stay).

Conclusions: Endovascular treatment of azygos vein in CCSVI patients appeared feasible and safe with a high rate of technical success.

Disclosures: The authors have nothing to disclose.

POROELASTIC MODEL OF GLYMPHATIC FLOW DRIVEN BY VASCULATURE PULSATION

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Recent experimental observations have shown the existence of a self-cleaning pathway within the central nervous system that removes metabolic waste products from the brain tissue. The natural pulsations of cerebral arteries and mechanotransduction of specialized glial cells facilitate the flow of some of the cerebrospinal fluid through the tissue from the penetrating arteries to the draining veins. This particular dynamics of the cerebrospinal fluid (CSF) is called glymphatic flow. Mathematical models and corresponding computer simulations are now needed to understand the mechanisms that govern the glymphatic flow. While peristaltic transport of Newtonian fluids through porous media can explain the flow of cerebrospinal fluid through the perivascular space, no mathematical models have been proposed yet for the glymphatic flow deeper in the brain tissue. We propose to investigate the mechanical response of brain tissue to arterial pulsations. We model the brain as a mixture of an elastically deformable solid phase made of brain cells and a Newtonian fluid phase made of cerebrospinal fluid. The environment is assumed to be axisymmetric with impermeable walls. Analytic expressions for the stream function and corresponding vorticity of the fluid phase are found from the linearized equations using perturbation theory. These results are then compared to numerical simulations. We conclude that there is non-zero vorticity around the arterial wall. Further studies are to be carried out coupling this model with the global circulation model of Mueller and Toro (2014).

Key words: Theory of mixtures; poroelasticity; glymphatic flow.

Disclosures: The authors have nothing to disclose.

SUBJECTS WITH JUGULAR ANOMALIES EXHIBIT INCREASED COLLATERAL VENOUS FLOW IN MRI

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Background: Jugular venous structure and flow anomalies have been shown in multiple sclerosis (MS) subjects compared to healthy controls (HC) using magnetic resonance imaging (MRI).

Objectives: A retrospective analysis of extracranial venous structure and function for a large cohort of MS patients and HC subjects.

Methods: A group of 571 MS subjects and 119 HC subjects were imaged with 3T MRI scanners. We assessed blood flow and anatomy of the extracranial vessels with phasecontrast flow quantification and magnetic resonance (MR) venographic imaging. Venous structures were classified by cranial drainage into three collateral types: Type I: internal jugular veins, Type II: paraspinal veins, and Type III: superficial veins. Jugular veins were classified into stenotic (ST) and nonstenotic (NST) groups. Individual, total vessel flow, as well as venous flow normalized to total arterial flow (tA) were quantified using in-house software. Comparisons in stenosis and

flow properties were made in MS, HC, and between their subcategories of stenosis type, location, and MStype.

Results: In the MS group, 352 (62%) classified as ST while 20 (22%) HC classified as ST ($X_2=59.3$, $P<0.05$). Type I and II normalized venous flow showed differences between the MS and HC groups ($P<0.05$ for type I and II), as well as between the NSTMS vs STMS ($P<0.05$ for type I and II), and HC vs STMS groups ($P<0.05$ for type I and II).

Conclusions: We were able to show with MRI that not only STMS exhibit IJV anomalies with reduced IJV flow, but that the flow in this cohort is elevated in the paraspinal venous collaterals (Type II). This property was observed in the STHC, but the prevalence of flow reduction in the HC group was significantly lower than the MS group.

Key words: MR venography; phasecontrast flow quantification; venous anatomy and flow.

Disclosures: The authors have nothing to disclose.

WHERE ARE WE IN UNDERSTANDING THE CAUSES OF NORMAL PRESSURE HYDROCEPHALUS?

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The objective of this presentation is to describe the evolution of causal explanations for NPH and to review the perspective for future efforts. NPH, which has idiopathic (iNPH) and secondary forms, results from disturbances in the interactions between the blood and cerebrospinal fluid (CSF) circulatory systems. Despite decades of clinical experience and research, there is scant understanding, especially for iNPH, of the underlying processes that trigger and sustain the disease. What we know today began with the first description of NPH, when Hakim proposed a hydraulic press theory to explain enlarged ventricles at normal intracranial pressure (ICP).^{1,2} A transient excess of CSF, which circulates through the CSF system by bulk flow, elevates intracranial pressure (ICP) and enlarges the ventricles, which remain enlarged due to Pascal's law when ICP normalizes. Subsequently, it was shown that enhanced choroid plexus pulsations, reflecting the cardiac cycle, are sufficient to enlarge ventricles.^{3,4} Over the next three decades, a dynamic view of CSF circulation developed. Pulsations of the major arteries into the brain are cushioned by cisternal CSF, resulting in an oscillatory flow of CSF between cranial and spinal subarachnoid spaces, smoothing pulsations into laminar flow at the capillaries (Windkessel effect). Subventricular capillaries are recognized as being a major site of CSF absorption across the ependyma, reducing the importance of drainage through the superior sagittal sinus. A chain of events is now proposed. Reduction of compliance of the craniospinal subarachnoid space, as with aging or trauma, elevates the arterial pulse pressure (including that of the choroid plexus), increases ICP, which compresses the dural sinuses and bridging veins, raising venous pressure and inhibiting CSF absorption via the SSS. These changes produce a stiffened, hyperdynamic brain and the energy of arterial pulsations is displaced to the subventricular capillary beds, disrupting them. The ventricles may thus expand without a pressure gradient between the ventricular walls and the subventricular space.⁵⁻¹¹ Bateman incorporates these principles into his venous hemodynamic theory of NPH.¹² He describes a positive feedback loop between the craniospinal compliance and cerebral venous pressure which eventually stops apical CSF drainage. Shunt placement breaks the feedback loop, restoring craniospinal compliance.¹² A simpler causal sequence is due to Bradley.^{13,14} He observes that a substantial percentage of iNPH patients are macrocephalic, likely due to childhood episodes of benign external hydrocephalus. As adults, these patients lose their ability to compensate for the hydrocephalus at a time when subventricular ischemic disease has diminished the absorption of CSF via the ependymal route. There are certainly alterations at the cellular and molecular levels which result in failure of critical biomechanical properties of the brain. The regulation of water via the aquaporins

merits attention,^{15,16} likewise gene identification from reverse genetics in the rare familial cases of iNPH.¹⁷ Refinements in magnetic resonance elastography (MRE) could better characterize brain biomechanical substrates.^{18,19} Prospective studies with presymptomatic patients would presumably simplify causal analysis. Insight into the causes and disease processes of NPH will lead to improved diagnosis and treatment and even, it is hoped, lead to preventive measures by identifying those at risk.

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ASSESSING THE CORRELATION BETWEEN IRON DEPOSIT IN THE BASAL GANGLIA AND FLOW ABNORMALITIES IN THE NECK VEINS WITH MRI: PRELIMINARY EXPERIENCE

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Background: In Multiple Sclerosis (MS), increased iron deposition has been demonstrated in the basal ganglia (BG), possibly related to dysfunction of the intracranial/extracranial venous drainage. Also,

ultrasound studies reported blood flow anomalies of the neck veins draining the intracranial compartment.

Objectives: To correlate BG R2* values, a measure of iron concentration, and the patterns of neck venous blood flow in patients with MS and healthy controls (HC) obtained with a single Magnetic Resonance (MR) study.

Methods: In 51 MS patients (age: 38±11 years; females: 67%) and 14 HC (age: 39±14 years; females: 70%) brain R2* maps were derived at 3T from a double-echo 3D Spoiled GRE (TR=28 ms, TE=7 and 22 ms, FA=20°) MR sequence. Using the FSL tool FIRST (Oxford, UK), mean R2* values were extracted in automatedly-segmented BG. In the same MR session, quantitative measures of the blood flow in the main neck arteries and veins were obtained at C2 and C6 levels, using a 2D phase-contrast sequence with peripheral retrospective triggering. Correlations were analyzed through IBM SPSS software among BG R2* values and Internal Jugular Vein (IJV) flow measures or an index of the activation of venous collaterals between C2 and C6 levels.

Results: In MS patients and HC, no significant correlations were found between BG iron deposition in any of the brain structures considered (head of caudate nucleus, pallidus, putamen and thalamus) and neither direct measures of IJV flow nor C2/C6 IJV flow mismatch index.

Conclusions: In this small cohort, the BG iron deposition in MS patients does not seem to be correlated with flow abnormalities in the veins of the neck. Further studies, possibly with quantitative assessment of the intracranial/extracranial flow in larger samples, are needed to investigate the cause of different iron accumulation rates in neurodegenerative disorders.

Key words: Multiple sclerosis; iron deposition; R2* map; jugular vein; extracranial venous flow.

PREVALENCE OF CHRONIC CEREBROSPINAL VENOUS INSUFFICIENCY IN MULTIPLE SCLEROSIS. RESULTS OF LARGE COHORT CASE-CONTROL STUDY

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Background: In phase 1 of chronic cerebrospinal venous insufficiency (CCSVI) prevalence study in multiple sclerosis (MS), we enrolled 499 subjects.¹ The CCSVI prevalence figures were 56.1% in MS, 42.3% in other neurologic diseases (OND), 38.1% in clinically isolated syndrome (CIS) and 22.7% in healthy controls (HC) (P<0.001). CCSVI prevalence was higher in progressive than in non-progressive MS patients (P=0.004).

Objectives: To cross-validate prevalence of CCSVI in phase 2 study of large cohort of patients with MS, CIS and OND and HCs, using specific proposed transcranial and extracranial echo-color Doppler (ECD) criteria.

Methods: In phase 1, ECD exams were carried by a single ECD technologist blinded to the subject disease status. In phase 2, ECD exams were carried out by two ECD technologists blinded to the subject disease status. In addition, in phase 2, subjects were positioned and covered with a blanket on the ECD chair by the unblinded study coordinator. A subject was considered CCSVI positive if ≥2 venous hemodynamic criteria were fulfilled.

Results: In total the CCSVI prevalence study included a total of 1014 subjects. Among those were 569 patients with MS, 78 with OND, 67 with CIS, 294 age- and sex-matched HCs and 6 subjects with radiologically isolated syndrome (RIS). In phase 2, 515 subjects consisting of 280 patients with MS, 52 with OND, 46 with CIS, 131 HCs and 6

subjects with RIS, were included. The CCSVI prevalence figures for Phase 2 study were: 63.2% in MS, 61.5% in OND, 56.5% in CIS, 34.4% in HC and 66.7% in RIS (P<0.001). The CCSVI prevalence figures for Phase 1 and 2 studies were: 59.6% in MS, 55.1% in OND, 50.7% in CIS, 27.9% in HC and 66.7% in RIS (P<0.001). In phase 2, CCSVI prevalence was higher in progressive than in non-progressive MS patients (P=0.004).

Conclusions: Our findings of phases 1 and 2 of CCSVI prevalence study are consistent with an increased prevalence of CCSVI in MS, CIS and OND patients compared to age- and sex-matched HCs, and in progressive MS patients compared to non-progressive ones. Phases 1 and 2 showed similar prevalence of CCSVI in the study groups.

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AN INTERIM ANALYSIS ON SUSCEPTIBILITY TO VASCULAR ALTERATIONS IN MS AND ALS

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Background: Among the factors contributing to brain damage in Multiple Sclerosis (MS), scientific evidences indicate ischemic changes, venous outflow abnormalities and accumulation of proinflammatory and neurotoxic substances.

Objectives: To study the association among MS, amyotrophic lateral sclerosis (ALS), and vascular changes at molecular, genetic, anatomical and functional level.

Methods: 300 MS patients, 50 ALS patients, and 300 healthy subjects (HS) will be recruited over 3 years. To assess the endothelial dysfunction development risk and/or a genetic susceptibility, serum levels and single nucleotide polymorphisms (SNP) of homocysteine, VEGF-A, Endothelin 1 (ET-1) and HIF1A will be analyzed and correlated to micro and macro vascular abnormalities detected by Magnetic Resonance (MR) and Ultrasound (US) imaging.

Results: Homocysteine levels (HL) were performed in 156 MS, 15 ALS patients and 145 HS, VEGF-A in 50 patients vs 25 HS. Median HL were 13.4 $\mu\text{mol/L}$ in MS, 12.82 $\mu\text{mol/L}$ in ALS patients and 12.6 $\mu\text{mol/L}$ in HS. At Kruskal-Wallis test median HL values were significantly different in the three groups ($P=0.002$). In particular, median HL were significantly higher in MS and ALS patients vs HS ($P<0.05$). In MS women median HL were significantly higher compared to HS (12 vs 9.94 $\mu\text{mol/L}$, $P<0.00001$), furthermore HL correlated to age in MS females. Median VEGF-A values tended to be higher in MS patients vs HS (9.68 vs 0, $P=0.196$). 101 patients (78 RR, 2 PP, 11 SP and 10 ALS) underwent contrast-enhanced brain MR, and 68 patients (54 RR, 1 PP, 10 SP and 3 ALS) underwent US evaluation.

Conclusions: Combining different molecular analysis and imaging modalities may provide new insights into the vascular aspects of MS pathogenesis. These preliminary results support an altered vascular profile in MS, especially in females, and ALS patients. Definitive results will be available at project termination in 2016.

Key words: Multiple sclerosis; endothelial factors; brain perfusion; intracranial circulation.

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THE FRAMINGHAM CARDIOVASCULAR RISK SCORE IN MULTIPLE SCLEROSIS

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Background: Different cardiovascular risk factors have been related to the risk of developing multiple sclerosis (MS), and to MS disability and course. However, it is possible that such factors interact variably, thus determining a global risk in MS subjects.

Objectives: We aim to compare the global cardiovascular risk of MS subjects with controls, and to evaluate its importance on MS-related disability, progression and treatment.

Methods: In our cross-sectional study design, age, gender, smoking status, body mass index, systolic blood pressure, diabetes, and use of antihypertensive medications have been recorded in MS subjects and controls to calculate the simplified 10-year Framingham General Cardiovascular Disease Risk Score (FR), an individualized percentage risk score estimating the 10-year likelihood of cardiovascular events.

Results: We recruited 265 MS subjects and matched 530 controls by propensity score. T-test showed similar FR between MS subjects and controls ($P=0.212$). Linear regression analysis showed a direct relationship between FR and Expanded Disability Status Scale ($P<0.001$) and MS Severity Scale ($P<0.001$). Analysis of variance showed a trend in reduced FR in Natalizumab when compared to Interferon,

Fingolimod or no current disease modifying treatment ($P=0.057$). T-test showed significantly higher FR in secondary progressive MS when compared to relapsing remitting MS ($P<0.001$).

Conclusions: The FR, evaluating the global cardiovascular health by the interaction among different risk factors, seems to be related to MS disability and progression. Modifiable cardiovascular risk factors should be carefully investigated and corrected with a possible effect on MS-related outcomes.

Key words: Multiple sclerosis; cardiovascular; Framingham; comorbidities.

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INCREASED ENDOTHELIN-1 SERUM LEVELS IN PATIENTS WITH MULTIPLE SCLEROSIS

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Background: Clinical and experimental evidence suggests that endothelin-1 (ET-1) plays a role in cardiac and vascular disease. Patients with multiple sclerosis (MS) show global cerebral hypoperfusion. The widespread decrease in perfusion in normal-appearing white matter and grey matter in MS seems to be secondary to increased blood concentrations of ET-1.

Objectives: To evaluate ET-1 in MS patients vs healthy subjects (HS) in the context of a larger study on the association among MS, amyotrophic lateral sclerosis (ALS), and vascular changes at molecular, genetic, anatomical and functional level.

Methods: ET-1 will be measured in 300 MS patients, 50 ALS patients, and 300 healthy subjects (HS) recruited over 3 years. Serum ET-1 levels were coded and assayed with a commercially available ELISA kit in blinded fashion by a laboratory assistant (detection range 0.39-25 pg/mL; R&D Systems).

Results: After two years we recruited 300 MS patients, 46 ALS patients and 178 HS. ET-1 levels were performed in 120 MS patients (79 females, 41 males) and in 125 HS (68 females, 57 males). ET-1 median were significantly higher in MS compared to HS (1.59 vs 1.50 pg/mL, $P=0.03$) at Mann-Whitney test. When stratified for gender, median ET-1 levels were significantly higher in females MS vs HS (1.58 vs 1.44 pg/mL, $P=0.03$). ET-1 levels positively correlated with age in female MS vs HS ($P<0.05$) but not in males. ET-1 median were significantly higher in 23 SP vs 97 RR MS subtype (2.10 vs 1.57 pg/mL, $P=0.003$).

Conclusions: We confirm that serum ET-1 levels are significantly increased in MS patients, especially in women. This finding could help to explain the higher incidence of MS in females and the sex-associated differences in susceptibility to cardiovascular diseases. Correlation of ET-1 levels with SP subtype of disease opens new insights in MS pathogenesis.

Key words: Multiple sclerosis; endothelial factors; ET-1.

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