Hypoperfusion of Brain Parenchyma is Strongly Associated with the Severity of Chronic Cerebrospinal Venous Insufficiency in Patients with Multiple Sclerosis

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Background

- Chronic cerebrospinal venous insufficiency (CCSVI) is a vascular condition described in multiple sclerosis (MS) patients, characterized by stenoses of the main extracranial veins with hampered cerebral venous outflow.
- These anomalies affect the internal jugular veins (IJV), the vertebral veins (VV) and the azygous vein (AZ), and can be detected using selective venography and extracranial venous Doppler. [1,2]
- Combined transcranial and extracranial echo-color Doppler (ECD) allows for non-invasive assessment of venous hemodynamic (VH) parameters indicative of CCSVI. [1,2]
- CCSVI diagnosis requires fulfillment of at least 2 out of 5 VH abnormal criteria.
- We hypothesized that the impaired venous outflow contributes to hypoperfusion of brain parenchyma.

Objectives

- To investigate the relationship between chronic CCSVI and cerebral perfusion in patients with MS.

Methods

- Sixteen consecutive relapsing-remitting MS patients (mean age 36.1yrs, mean disease duration 7.5yrs and median EDSS 2.5) and 8 age-and sex-matched normal controls (NC) were scanned on a GE 3T scanner using dynamic susceptibility contrast-enhanced perfusion-weighted imaging (PWI) (Table 1). [3]
- All subjects were examined on a 3T GE Signa Excite HD 12.0 Twin Speed 8-channel scanner (General Electric, Milwaukee, WI). A multi-channel head and neck (HDNV) coil manufactured by GE was used to acquire the following sequences: 2D multi-planar dual fast spin-echo (FSE) proton density (PD) and T2-weighted image (WI); Fluid-Attenuated Inversion-Recovery (FLAIR); 3D high resolution (HIRES) T1-WI using a fast spoiled gradient echo (FSPGR) with magnetization-prepared inversion recovery (IR) pulse, SE T1-WI both with and without a single dose intravenous bolus of 0.1 mMol/Kg Gd-DTPA 5 min after injection and perfusion-weighted imaging (PWI). Scans were prescribed in an axial-oblique orientation, parallel to the subcallosal line.
- PWI was acquired during and after injection of Gd-DTPA (15mL 0.1 mmol/kg) with an MRI-compatible power injector at a speed of 5 ml/s. The NC were also injected with the contrast agent. Single-shot gradient-echo EPI was used with the following parameters: TR 2275 ms, TE 45 ms, FOV 26 x 26 cm, matrix 96 x 96 (resulting in inplane voxel sizes of 2.71 x 2.71 mm), 20 slices (7 mm thick) with no gap. Forty time points were acquired per slice.
- PWI characteristics of the various regions studied, including deep gray matter structures and gray matter (GM) and white matter (WM) tissue compartments were assessed.
- Calculation of perfusion cerebral blood flow (CBF), blood volume (CBV) and mean transit time (MTT) was conducted using a previously described technique. [4] Briefly, we used the Java Image Manipulation software package (Xinapse Systems, Thorpe Waterville, UK) [5] with an automated AIF-finding algorithm and singular value decomposition for perfusion curve fitting. CBF and CBV values were relative, based on estimated tissue relaxivity parameters.

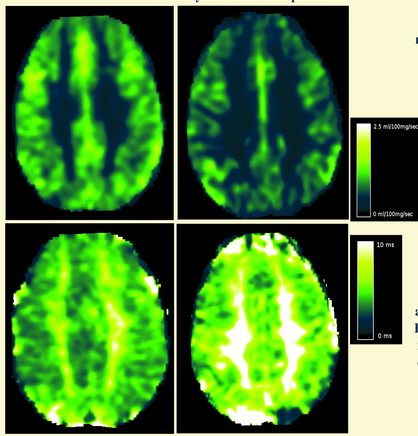
Table 1. Demographic, clinical, venous hemodynamic and MRI characteristics of relapsing-remitting MS patients and healthy controls.

	Multiple Sclerosis (n-16)	Healthy Controls (n=8)	p
Female gender, n (%)	10 (63%)	6 (75%)	NS
Age in years, mean (SD)	36.1 (7.3)	33.1 (7.3)	NS
Disease duration, mean (SD)	7.5 (1.9)	---	---
Age at diagnosis, mean (SD)	35.8 (9.2)	---	---
Expanded Disability Status Scale, mean (SD)	2.4 (0.9)	---	---
Multiple Sclerosis Functional Composite, mean (SD)	-2.5 (0.03)	-2.5 (0.02)	NS
Treatment in years, mean (SD)	4.3 (3.4)	---	---
Distribution of VH criteria			
VH1	12 (75%)	0 (0%)	<0.001
VH2	14 (88%)	0 (0%)	
VH3	14 (88%)	1 (13%)	
VH4	13 (81%)	0 (0%)	
VH5	8 (50%)	0 (0%)	
Number of venous hemodynamic criteria, mean (SD)	3.8 (0.23)	0.12 (0.35)	<0.001
Venous Hemodynamic Insufficiency Severity Score, mean (SD)	8.9 (2.8)	0 (0)	<0.001

The differences between MS patients and healthy controls were assessed using the Student's t-test, Fisher Exact test and Mann-Whitney rank sum test.

- Correction for patient motion prior to perfusion analysis was performed using FMRIB's Linear Image Registration Tool for Motion Correction (MCFLIRT). [6]
- Using the first steady-state volume before contrast arrival time, we applied FMRIBs Linear Image Registration Tool (FLIRT) to derive an affine matrix providing a transformation from the native perfusion acquisition space to the high-resolution FLAIR space. This matrix was then used to co-register perfusion MTT, CBF, and CBV maps into the subject-specific upsampled FLAIR space. These maps were then overlaid onto all relevant ROI masks to calculate mean values for MTT, CBF, and CBV within each tissue compartment and each deep gray matter structure. The perfusion was measured in the GM, WM, thalamus, pulvinar nucleus of thalamus, caudate, putamen, globus pallidus, hippocampus, amygdala, nucleus accumbens, red nucleus and substantia nigra.
- A diagnosis of CCSVI was established based on the VH Doppler criteria 2 and the severity was based on fulfilled the VH criteria (score 0-5) and VH insufficiency severity score (VHISS) (score 0-16). [3]
- Correlation analysis (Spearman) was used to assess the relationship between PWI measures and VH, VHISS. No correction for multiple comparisons was performed for correlation analyses, given the exploratory nature of the study and low sample size. We considered p<0.05 as significant.

Figure. Examples of perfusion imaging maps in 2 relapsing-remitting multiple sclerosis patients with severe (right images) and less severe (left images) venous hemodynamic insufficiency severity score (VHISS). On the left side is a 33 year old RRMS patient with VHISS 5, and on the right is a 38 year old RRMS patient with VHISS 12.



The upper row images represent cerebral blood flow (CBF) results with the dark areas indicating lower CBF flow. Please note more dark areas in the white and gray matter on the right compared to the left image.

The lower row images represent mean transit time (MTT) results with bright areas indicating higher MTT. Please note more bright areas in the white and gray matter on the right compared to the left image.

Results

- All 16 MS patients fulfilled the diagnosis of CCSVI (median VH=4, median VHISS=9) and none of the NC (Table 1).
- There was a significant association between VH criteria and VHISS, and CBF, CBV and MTT in all examined regions of the brain parenchyma in MS patients (Table 2).
- The most robust correlations were observed for lower CBF and higher VHISS in the GM and WM (r= -0.70 to -0.72, p<0.002) (Figure), and in the thalamus, caudate, putamen, hippocampus and nucleus accumbens (r= -0.6 to-0.72, p<0.008). The correlation coefficients for CBV and MTT were somewhat lower.
- No relationship was observed for NC between VH and VHISS and PWI outcomes.

Conclusion

- This study demonstrates that the severity of CCSVI is strongly associated with hypoperfusion of the brain parenchyma in MS.

Disclosure

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Table 2. Spearman correlation coefficients and p values between venous hemodynamic insufficiency severity score (VHISS) and perfusion-weighted (PWI) measures (in bold are highlighted significant correlations) in relapsing-remitting patients.

	Mean transit time		Cerebral blood flow		Cerebral blood volume	
	r	p	r	p	r	p
Gray matter	**0.52**	**0.039**	**-0.70**	**0.002**	**-0.58**	**0.019**
White matter	**0.53**	**0.034**	**-0.71**	**0.002**	-0.49	0.054
Right caudate	0.44	0.087	-0.45	0.078	-0.23	0.387
Left caudate	**0.53**	**0.033**	-049	0.065	-0.33	0.214
Right putamen	0.45	0.084	**-0.70**	**0.003**	-0.39	0.135
Left putamen	0.45	0.077	**-0.71**	**0.002**	-0.39	0.140
Right globus pallidus	0.37	0.154	**-0.68**	**0.003**	-0.31	0.251
Left globus pallidus	0.43	0.099	**-0.69**	**0.003**	-0.13	0.627
Right thalamus	0.46	0.074	**-0.66**	**0.006**	**-0.51**	**0.044**
Left thalamus	0.46	0.077	**-0.66**	**0.006**	**-0.61**	**0.012**
Right pulvinar thalamus	0.17	0.528	**-0.67**	**0.004**	**-0.59**	**0.025**
Left pulvinar thalamus	**0.55**	**0.027**	**-0.67**	**0.005**	-0.47	0.067
Right hippocampus	0.40	0.123	**-0.59**	**0.015**	-0.43	0.099
Left hippocampus	0.34	0.198	**-0.61**	**0.013**	-0.49	0.053
Right amygdala	0.05	0.856	-0.37	0.159	-0.44	0.085
Left amygdala	0.16	0.547	**-0.51**	**0.045**	-0.41	0.123
Right accumbens	0.48	0.059	**-0.55**	**0.028**	-0.14	0.608
Left accumbens	**0.52**	**0.041**	**-0.64**	**0.008**	-0.27	0.305
Right red nucleus	0.37	0.156	-0.54	0.033	-0.43	0.099
Left red nucleus	0.32	0.234	-0.54	0.029	-0.46	0.075
Right substantia nigra	0.13	0.627	-0.59	0.017	-0.31	0.251
Left susbstantia nigra	0.19	0.481	-0.53	0.034	-0.16	0.565

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