Multiple Sclerosis Journal
http://msj.sagepub.com/

Non-specific alterations of craniocervical venous drainage in multiple sclerosis revealed by cardiac-gated phase-contrast MRI

Birgit Ertl-Wagner, Inga Koerte, Tania Kümpfel, Astrid Blaschek, Ruediger P Laubender, Max Schick, Denise Steffinger, David Kaufmann, Florian Heinen, Maximilian Reiser, Noam Alperin and Reinhard Hohlfeld

Mult Scler 2012 18: 1000 originally published online 22 December 2011
DOI: 10.1177/1352458511432742

The online version of this article can be found at:
http://msj.sagepub.com/content/18/7/1000

Published by:
SAGE
http://www.sagepublications.com

Research Paper

MULTIPLE SCLEROSIS JOURNAL | MSJ

Multiple Sclerosis Journal
18(7) 1000–1007

DOI: 10.1177/1352458511432742
msj.sagepub.com
SAGE

Non-specific alterations of craniocervical venous drainage in multiple sclerosis revealed by cardiac-gated phase-contrast MRI

Birgit Ertl-Wagner[1], Inga Koerte[1], Tania Kümpfel[2], Astrid Blaschek[3], Ruediger P Laubender[4], Max Schick[1], Denise Steffinger[1], David Kaufmann[1], Florian Heinen[3], Maximilian Reiser[1], Noam Alperin[5] and Reinhard Hohlfeld[2]

Abstract

Objective: There is an on-going controversy about venous drainage abnormalities in multiple sclerosis (MS). We applied cardiac-gated phase-contrast and venographic magnetic resonance (MR) techniques to compare venous drainage patterns in patients with MS, healthy controls, and subjects with migraine.

Methods: A total of 27 patients with MS (21 female, age 12–59 years, mean disease duration 8.4 ± 8.5 years) and 27 age- and gender-matched healthy controls (21 female, age 12–60 years) were investigated with velocity-encoded cine-phase contrast MR sequences and a 2D time-of-flight MR venography of the cervicocranial region on a 3-T MRI. The data were compared with 26 patients with chronic migraine headaches (19 female, age 17–62 years), previously investigated with the same protocol. The degree of primary and secondary venous outflow in relation to the total cerebral blood flow (tCBF) was compared both quantitatively and qualitatively. Statistical analyses were performed using linear regression models.

Results: Secondary venous outflow was significantly increased in patients with MS compared with healthy controls, both qualitatively ($p < 0.001$) and quantitatively ($p < 0.013$). The observed changes were independent of age and disease duration. Very similar alterations of venous drainage were detectable with the same approach in patients with migraine, without significant differences between MS and migraine patients ($p = 0.65$).

Conclusion: Our MRI-based study suggests that patients with MS have alterations of cerebral venous drainage similar to subjects with chronic migraine. These non-disease-specific changes seem to a secondary phenomenon rather than being of primary pathogenic importance.

Keywords

multiple sclerosis, phase-contrast imaging, secondary venous channels, venous drainage

Date received: 1st November 2011; revised: 15th November 2011; accepted: 18th November 2011

Introduction

Possible alterations of craniocervical venous drainage patterns continue to receive extraordinary attention in multiple sclerosis (MS) research.[1-5] While a chronically impaired venous drainage with a consecutive opening of collateral venous channels, referred to as cerebrospinal venous insufficiency (CCSVI), had initially been described as a finding specific to MS with positive and negative predictive values of 100%,[6,7] these high sensitivity and specificity values have not been reproduced. Nevertheless, CCSVI was even postulated to play a causative role in MS,[6,8] and taken as justification for interventional percutaneous transluminal angioplasties.[9-11] However, these endovascular treatments

[1]Institute of Clinical Radiology, University of Munich – Grosshadern Campus, Ludwig-Maximilians-University Munich, Germany.
[2]Institute of Clinical Neuroimmunology, Ludwig-Maximilians-University Munich, Germany.
[3]Department of Pediatric Neurology and Developmental Medicine, Dr. von Hauner's Children's Hospital, Ludwig-Maximilians-University Munich, Germany.
[4]Institute of Medical Informatics, Biometry, and Epidemiology (IBE), Ludwig-Maximilians- University Munich, Germany.
[5]Department of Radiology, Miller School of Medicine, University of Miami, USA.

Corresponding author:
Birgit Ertl-Wagner, MD, Institute of Clinical Radiology, Ludwig-Maximilians-University, Marchioninistrasse 15, 81377 Munich, Germany.
Email: birgit.ertl-wagner@med.uni-muenchen.de

have led to serious adverse events.[12] Therefore, thorough investigations of the patterns of craniocervical venous drainage in MS are warranted.

Recently, several studies have questioned the existence of CCSVI altogether, since they found no alterations in cerebrospinal venous drainage in patients with MS using various techniques including Doppler sonography and MRI.[12-14] A recently published, large Doppler-sonographic study, however, reported an increased presence of CCSVI in patients with MS, albeit with modest sensitivity and specificity.[4]

Overall, controversy prevails regarding the presence and significance of CCSVI in MS, and the subject continues to draw attention in the media. Further studies with standardized and operator-independent approaches are warranted to further clarify this disagreement. In light of the current controversy, we aimed to both quantitatively and qualitatively evaluate the craniocervical venous drainage patterns in a cohort of MS patients with a wide range of age and disease duration, in comparison to age- and gender-matched healthy controls, using MR-based venographic and cardiac-gated cine-phase contrast techniques in a highly standardized fashion. Moreover, we aimed to quantitatively compare the venous drainage patterns of patients with MS to a cohort with chronic migraine headaches previously studied with the same imaging protocols and post-processing algorithms.[15]

Subjects and methods

Subjects with MS and respective controls

Twenty-seven patients with MS were included. Age ranged from 12 to 59 years, median age was 25.35 years (1st quartile: 16.82; 3rd quartile: 36.42). Nine patients (30%) were younger than 18 years. A total of 21 (77.8%) subjects were female. The median duration of disease since diagnosis was 5.0 years (1st quartile: 2.5; 3rd quartile: 12.0); disease duration was less than or equal to 2 years in eight patients. Inclusion criteria were a diagnosis of MS according to the revised McDonald criteria,[16] disease duration of at least 6 months and absence of additional neurological disorders. Exclusion criteria were magnetic resonance (MR)-related contraindications.

The control group consisted of 27 age- and gender-matched healthy subjects (age ranged from 11 to 60 years, median age 25.57 years [1st quartile: 16.44; 3rd quartile: 36.03]; 21 female [22.2%]). Inclusion criteria were the absence of any neurological disorder, while exclusion criteria consisted of MR-related contraindications.

Approval by the local institutional review board was obtained and informed consent was given by all study participants.

Subjects with migraine and respective controls

The MS cohort was compared with subjects with migraine previously investigated with the same methodology.[15] The migraine cohort consisted of 26 subjects (age ranged from 17 to 62 years, mean age 37.3 ± 13.9, 19 female) with recurrent episodic migraine without aura (on 0.1 to 6 days/month for 16.6 ± 11.7 years) according to the International Classification of Headache Disorders.[17] The respective age- and gender-matched control cohort consisted of 26 subjects (age ranged from 17 to 60 years, mean age 37.3 ± 13.7; 19 female).

Image acquisition

All subjects underwent MRI on a 3-T MR scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany), using a 12-element phased-array head coil. 3D magnetization-prepared rapid-acquisition gradient echo (MP-RAGE) imaging was obtained for structural information using the following parameters: TR 11 ms, TE 4.76 ms, field of view (FOV) 230 mm, voxel size = 1 × 1 × 1 mm^3, iPAT, acceleration factor 2. A total of 160 sagittal slices were acquired, covering the entire brain. Fluid-attenuated inversion recovery (FLAIR) sequences were obtained using the following parameters: TR 94 ms, TE 6500 ms, field of view 250 mm, voxel size = 0.98 × 0.98 × 3 mm^3, distance factor 10%, fat saturation. Forty-five axial slices were acquired covering the entire brain.

To visualize primary and secondary venous channels, a 2D time-of-flight MR venography of the infratentorial and upper cervical regions was performed (slice thickness 2.0 mm, FOV 160 mm, TR 23 ms, TE 5.43 ms and FA 40°). MR-venographic datasets were available for 21 MS patients and 25 controls.

To measure blood flow to and from the skull, two retrospectively gated, velocity-encoded cine-phase contrast scans were acquired (FOV 140 mm, matrix 256 × 179, voxel size 0.8 × 0.5, slice thickness 4 or 6 mm, TR 40 ms, TE 4.05 ms, FA 20°, acquisition time: 32 completely acquired cardiac cycles equalling approximately 3 minutes depending on the individual heart rate). First, a high-velocity encoding (VENC 70 cm s^{-1}) was used to quantify the high-velocity blood flow in the internal carotid arteries (ICAs), vertebral arteries (VAs), internal jugular veins (IJVs) and secondary veins. The imaging slab was located at the level of upper C2 with an orientation perpendicular to the main four arteries (ICA and VA bilaterally) and the IJVs.[18] To allow for the low-velocity secondary venous flow (SVF) a sequence with low-velocity encoding (VENC 7–9 cm s^{-1}) was acquired at the same level. A 2D time-of-flight MR angiography was used as a localizer to ascertain the correct positioning. Quantitative velocity-encoded datasets were available for all patients and controls.

Post-processing and data analysis

The MRI datasets were examined for image quality and head movement. Time-dependent volumetric flow rates

were calculated by integrating the flow velocities inside the luminal cross-sectional areas over all 32 images using the pulsatility-based segmentation of lumens conducting non-steady flow algorithm.[19] Mean flow rates were obtained for each of the four main cervical arteries (left and right internal carotid artery [LICA, RICA] and left and right vertebral artery [LVA, RVA]), for the primary venous pathways (left and right internal jugular vein [LIJV, RIJV], and the secondary venous pathways: vertebral veins [VVs], epidural veins [EVs], and deep cervical veins [DCVs]). Total cerebral blood flow (tCBF) and total jugular venous flow (JVF) were obtained by summation of the flows through the four arteries (LICA + RICA + LVA + RVA) and the two IJVs, respectively. SVF was defined as the sum of the flow through the three main secondary channels (VV + EV + DCV). The SVF and the JVF were also calculated as a percentage of the tCBF. Given the fact that the blood entering the brain needs to be draining from it as well, the difference between the tCBF and the sum of the detected venous drainage (tCBF – (IJV + VV + EV + DCV)) was considered as the unmeasured secondary venous outflow. It was calculated as a percentage of the individual tCBF. Each cardiac cycle results in a rather small amount of CSF net flow along the spinal canal.[20] Owing to the small amount of the CSF flow in relation to the large volumes of arterial inflow and venous outflow, the CSF flow was not taken into account in this study. All analyses were done with the software MRICP version 1.4.35 (Alperin Noninvasive Diagnostics, Miami, FL).

Three-dimensional models of the MRVs were reconstructed using the maximum intensity projection technique. The MRV source images and the respective maximum intensity projections were then visually analyzed to determine the degree of secondary venous outflow (1 no; 2 minimal; 3 mild secondary venous outflow; and 4 pronounced secondary venous outflow in one of the three pathways (VV, EV or DCV); 5 secondary venous outflow in two of the three pathways; and 6 secondary venous outflow in all three pathways) by a board certified neuroradiologist who was blinded to the subjects' clinical status. In addition, the FLAIR sequences of all MS patients, healthy controls and migraine patients were evaluated for the presence of pathological white matter lesions or other structural abnormalities of the brain.

Statistical analyses

Owing to the small sample size, adequate measures of location and spread were calculated; the non-parametric test (Mann–Whitney *U*-test) was used to test for group differences and Spearman's correlation coefficient was used for quantifying relationships between variables. For testing the influence of possible confounders (age, gender, medication, type of MS, duration of illness) linear regression models were used where some of the clinical endpoints were adequately transformed to satisfy the normality and homoscedasticity assumptions. Further, we used fractional polynomials to test for possible non-linear relationships between an endpoint and continuous confounders.[21] Finally, graphically based residual analyses were performed to check whether the assumptions of the linear regression models were fulfilled. Further, linear regression models for modelling SVF and SVF/TCBF were used to test for differences between the MS group and the migraine group. In addition, we tested for differences between healthy controls and the three patient groups. These models were adjusted for age and gender. A p-value below 0.05 (two-sided) was considered statistically significant. All statistical analyses were performed with R (version 2.12.2).

Results

Venous drainage in MS compared with age- and gender-matched healthy controls

The amount of venous drainage through secondary channels as a percentage of the individual tCBF was significantly higher for MS patients compared with controls (patients: median 11.81%, 1st quartile 4.36% and 3rd quartile 18.67% versus controls: median 2.27%, 1st quartile 1.57% and 3rd quartile 6.68%; $p = 0.0005$). Linear regression models demonstrated no significant effect of age or disease duration on the abnormal venous drainage pattern.

Visual analysis of the 3D models of the venous outflow demonstrated an augmented (grade 4–6) secondary extracranial venous drainage in 15/21 MS patients versus in 3/25 controls ($p < 0.0001$). A significant correlation between MR venography grading and measured secondary venous outflow was demonstrated using the Spearman's rho correlation coefficient ($p < 0.0001$; rho = 0.73).

Table 1 summarizes the results. Figure 1 shows an example of the maximum intensity projections of cerebrovenous drainage in a patient with MS and a subject with migraine compared to healthy controls.

Comparing venous drainage in MS and migraine

A linear regression model revealed no significant differences of secondary venous drainage between the MS group and the migraine group ($p = 0.65$). Moreover, no significant differences were found between the patient cohorts regarding the secondary venous drainage as a percentage of the tCBF (MS versus migraine 0.23). However, when the MS and migraine cohorts were compared with age- and gender-matched healthy controls, both patient cohorts showed significantly increased relative secondary venous drainage (MS versus controls: $p = 0.004$; migraine versus controls: $p = 0.02$; compare Figure 2). Visual analysis of axial FLAIR

Table 1. Overview of the results obtained in 27 multiple sclerosis patients (MS) and 27 age- and gender-matched healthy controls (CTR). Age and gender are listed in columns 2 and 3; JVF: jugular venous flow through the right and the left internal jugular vein given as a percentage of total cerebral blood flow (tCBF); measured secondary venous flow is defined as the sum of venous blood flow through the left and right epidural, deep cervical and vertebral veins and is given as percentage of tCBF; DCV: secondary venous flow through deep cervical veins in percentage of tCBF; VV%: secondary venous flow through vertebral veins in percentage of tCBF; EV%, secondary venous flow through epidural veins as a percentage of tCBF; unmeasured secondary venous flow is defined as the difference between tCBF and JVF plus measured secondary venous flow. MRV: rating of magnetic resonance (MR) venography from 1 (no secondary venous outflow) to 6 (pronounced secondary venous outflow through the three main secondary venous pathways). Mean values for both cohorts are shown at the bottom of each column; *p*-values denote significance of any difference between MS and CTR. *p*-values are not given for each of the secondary pathways due to the low number of observations.

ID	Age years	Gender	JVF total %	Secondary venous outflow						
				Measured				Unmeasured volume %	MRV grading	Time since Diagnosis/ years
				total %	*DCV %*	*VV %*	*EV %*			
MS_01	12.0	f	64.9	19.0	*13.8*	*4.1*	*1.0*	15	5	2
MS_02	13.2	m	78.4	18.4	*10.7*	*6.8*	*0.8*	2	3	6
MS_03	14.2	m	102.7	2.7	*0.0*	*0.0*	*2.7*	0	n.a.	1
MS_04	14.7	f	58.1	27.9	*25.4*	*0.0*	*2.5*	14	n.a.	1
MS_05	15.2	f	66.1	11.8	*5.2*	*6.0*	*0.6*	21	n.a.	1
MS_06	16.5	f	0.0	48.9	*21.0*	*0.0*	*27.9*	51	5	4
MS_07	16.8	m	87.9	8.8	*1.6*	*2.7*	*4.4*	3	3	2
MS_08	16.9	f	42.5	19.3	*11.9*	*4.0*	*3.4*	37	n.a.	3
MS_09	17.1	f	76.2	0.0	*0.0*	*0.0*	*0.0*	24	n.a.	3
MS_10	19.9	m	52.0	7.0	*5.2*	*1.8*	*0.0*	41	5	2
MS_11	23.5	f	61.1	3.0	*3.0*	*0.0*	*0.0*	35	2	3
MS_12	23.7	m	66.8	12.3	*4.9*	*2.5*	*4.9*	21	5	2
MS_13	24.9	f	75.7	10.7	*4.2*	*3.2*	*3.2*	13	4	6
MS_14	25.4	f	83.7	0.0	*0.0*	*0.0*	*0.0*	15	2	8
MS_15	28.5	f	87.1	2.5	*1.5*	*0.0*	*1.1*	9	4	6
MS_16	30.2	f	56.1	40.6	*23.2*	*0.0*	*17.4*	2	5	0.04
MS_17	30.9	f	71.2	3.4	*3.4*	*0.0*	*0.0*	25	n.a.	4
MS_18	31.2	f	0.0	83.4	*75.6*	*0.0*	*7.8*	15	5	5
MS_19	34.1	f	69.6	18.0	*11.5*	*5.6*	*0.9*	12	4	11
MS_20	34.8	f	85.8	4.7	*0.5*	*4.2*	*0.0*	9	4	12
MS_21	38.1	f	76.7	5.3	*5.3*	*0.0*	*0.0*	17	3	5
MS_22	42.5	f	74.5	4.0	*3.0*	*0.0*	*1.0*	21	3	12
MS_23	43.8	f	52.4	15.3	*10.6*	*2.4*	*2.2*	31	5	13
MS_24	45.3	f	57.1	17.3	*12.8*	*0.0*	*4.5*	26	5	14
MS_25	46.6	f	78.6	7.1	*7.1*	*0.0*	*0.0*	14	5	21
MS_26	50.9	m	68.4	15.6	*11.2*	*1.2*	*3.2*	16	5	30
MS_27	59.6	f	25.5	38.4	*21.7*	*0.0*	*16.6*	35	5	30
CTR_01	11.7	f	76.7	2.1	*2.1*	*0.0*	*0.0*	20	1	
CTR_02	13.7	m	80.0	2.2	*1.3*	*0.0*	*0.9*	18	1	
CTR_03	14.5	m	81.0	3.3	*0.5*	*2.0*	*0.8*	15	2	
CTR_04	14.4	f	54.0	6.8	*3.1*	*0.0*	*3.7*	39	3	
CTR_05	15.2	f	79.3	15.0	*9.7*	*3.6*	*1.7*	6	4	
CTR_06	16.1	f	89.1	6.5	*2.3*	*0.0*	*4.3*	4	2	
CTR_07	16.1	m	53.0	14.7	*7.6*	*4.2*	*2.8*	32	4	
CTR_08	16.7	f	55.0	5.1	*0.0*	*5.1*	*0.0*	39	3	
CTR_09	17.0	f	81.3	2.3	*1.4*	*0.0*	*0.9*	15	1	
CTR_10	17.9	m	105.7	1.1	*0.2*	*0.0*	*0.9*	0	1	
CTR_11	23.9	f	65.4	1.2	*1.2*	*0.0*	*0.0*	33	1	
CTR_13	24.9	m	92.9	8.0	*1.0*	*4.7*	*2.2*	0	1	

(Continued)

Table 1. (Continued)

ID	Age years	Gender	JVF total %	Secondary venous outflow						
				Measured				Unmeasured volume %	MRV grading	Time since Diagnosis/ years
				total %	*DCV %*	*VV %*	*EV %*			
CTR_12	24.6	f	83.2	0.4	*0.0*	*0.0*	*0.4*	16	2	
CTR_14	25.6	f	92.0	1.0	*1.8*	*0.0*	*0.8*	7	1	
CTR_15	28.6	f	61.2	7.8	*7.8*	*0.0*	*0.0*	30	3	
CTR_16	29.2	f	77.8	3.6	*1.1*	*0.0*	*2.6*	20	2	
CTR_17	30.1	f	81.8	1.5	*1.5*	*0.0*	*0.0*	16	2	
CTR_18	32.7	f	71.5	2.2	*1.5*	*0.0*	*0.7*	27	3	
CTR_19	33.7	f	76.5	2.2	*2.2*	*0.0*	*0.0*	21	2	
CTR_20	34.9	f	72.9	3.6	*1.5*	*0.0*	*2.1*	23	4	
CTR_21	37.2	f	74.1	4.6	*1.6*	*0.0*	*3.0*	19	n.a.	
CTR_22	41.4	f	77.6	0.7	*0.0*	*0.0*	*0.7*	21	2	
CTR_23	44.7	f	43.2	17.0	*11.3*	*1.3*	*4.3*	39	n.a.	
CTR_24	45.5	f	84.1	1.3	*0.8*	*0.0*	*0.5*	14	2	
CTR_25	45.6	f	62.5	1.8	*0.0*	*0.0*	*1.8*	36	2	
CTR_26	49.5	m	60.6	16.3	*7.9*	*5.4*	*3.0*	23	2	
CTR_27	60.6	f	77.9	1.7	*1.7*	*0.0*	*0.0*	20	2	
Mean	**MS**	**2**	**63.7**	**16.5**	**10.9**	**1.6**	**3.9**	**19.4**	**4.1**	**7.7**
	CTR		**74.5**	**5.0**	**2.6**	**1.0**	**1.4**	**20.5**	**2.1**	
***p*-value**			**0.010**	**0.001**				**0.100**	**0.004**	

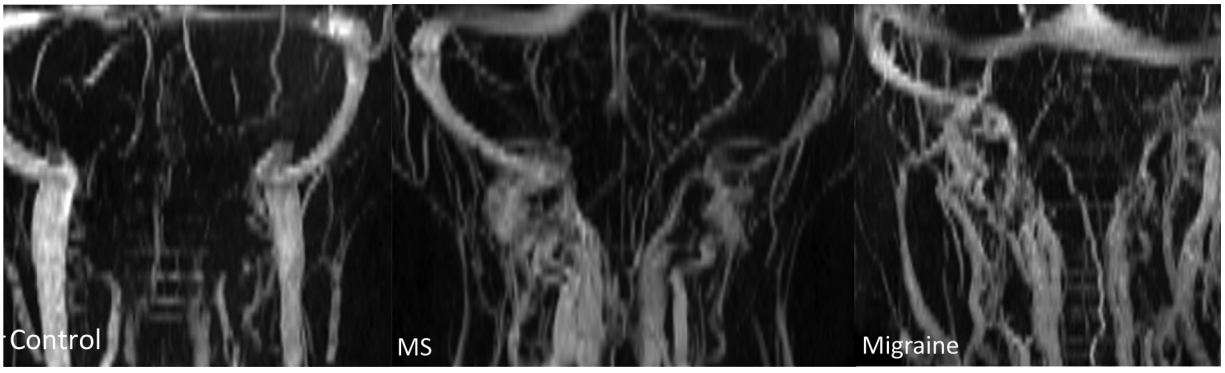

Figure 1. Representative examples of magnetic resonance venographic images from a healthy control (left), patient with multiple sclerosis (middle), and subject with migraine (right). Compared with the controls, there is a marked increase of secondary venous drainage in the multiple sclerosis patient and the subject with migraine.

sequences in the subjects with migraine and in the healthy controls did not reveal any pathological white matter lesions or other structural brain abnormalities in any of these subjects. In contrast, MS-typical lesions of the white matter fulfilling the revised McDonald criteria were present in all MS patients.

Discussion

Using a quantitative MR-based approach, we observed a significant difference in craniocervical outflow patterns with increased secondary venous drainage in a substantial proportion of MS patients as compared to healthy controls. However, as we observed similar changes in subjects with a history of migraine, we consider these alterations in drainage patterns not to be specific for MS. A primary role of altered venous drainage in the pathogenesis of MS therefore appears unlikely.

Similar to our findings, a recent Doppler-sonographic study by Zivadinov et al. reported CCSVI-related changes in a proportion of MS patients compared with healthy controls.[4] The reported prevalence of CCSVI was 62.5% for

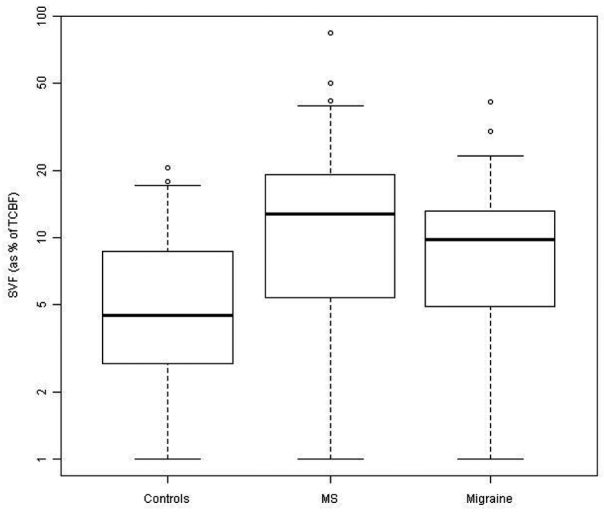

Figure 2. Comparison of secondary venous outflow in healthy controls, multiple sclerosis patients and subjects with migraine. Whisker plots display the measured secondary venous outflow as a percentage of total cerebral blood flow (tCBF) for the three groups: controls (all healthy controls), MS (patients with multiple sclerosis) and migraine (subjects with migraine). Compared with the cohort of all healthy controls, the secondary venous outflow relative to tCBF was significantly increased in both, the MS and migraine cohorts. No significant differences were found between the patient cohorts (MS versus migraine $p = 0.23$). Circles above a whisker plot mark outliers.

MS, 45.8% for other neurological disorders, and 25.5% for healthy controls when borderline cases were excluded ($p < 0.001$).[4] In this Doppler-based study, the control group was more heterogeneous than in our MR-based study, and contained only one case of migraine.[4] This might explain the differences between the two studies with regard to the prevalence of craniocervical venous drainage abnormalities in controls. Another study, however, reported no differences between MS patients and controls in a cohort of 21 MS patients and 20 healthy controls regarding internal jugular venous outflow and aqueductal flow using phase-contrast sequences and contrast-enhanced MR angiography; jugular venous stenosis was observed in 3 patients with MS.[22] In addition to CCSVI, iron deposition in the brain has been in the focus of interest in MS research in recent years. A pilot case–control study described a correlation between an increase in cerebral iron concentration and sonographic evidence for abnormal venous drainage.[23] On the other hand, diminished visibility of the cerebral venous vasculature on susceptibility-weighted imaging would argue against cerebral venous engorgement.[24]

In our study, we applied MRI to qualitatively and quantitatively evaluate the pattern of primary and secondary venous outflow. Different from other studies, we did not primarily focus on the presence or absence of CCSVI per se, but rather on the absolute and relative quantification of blood flow in the craniocervical venous channels. Moreover, we focused on the upper craniocervical venous drainage and not on the intracranial veins.

Cardiac-gated cine-phase contrast sequences with a pulsatility-based segmentation algorithm allow a quantification not only of the venous outflow in the various primary and secondary channels, but also of the arterial blood flow.[25] Therefore, quantification of the relative secondary venous outflow in relation to the tCBF can be performed. The methodology of the pulsatility-based segmentation of lumens conducting non-steady flow has been shown to be superior to manual segmentation techniques in quantifying time-dependent volumetric flow rates.[19] This method is largely operator-independent and can therefore serve as an objective tool for analyzing craniocervical venous flow patterns.[19] We considered this objectivity of flow quantification to be important in the light of the currently prevailing controversy. In addition to the quantitative methodology, a visual analysis of the craniocervical venous outflow was performed and graded semi-quantitatively.

In a recent MR-based study no reflux in the internal cerebral veins and/or straight sinus was observed, suggesting abnormalities in venous drainage reflect anatomical variants rather than clinically relevant venous outflow obstructions.[3] By comparison, our study revealed a difference between MS patients and healthy controls, both for the quantitative assessments of venous outflow in the secondary venous channels and of the secondary venous outflow in relation to the tCBF, and for the qualitative visual assessment of the MR-venographic craniocervical pattern. In contrast to the study by Wattjes et al.,[3] we did not investigate the intracranial flow, but rather focused on the extracranial outflow. Comparing the results of the two studies, we postulate that the alterations in venous outflow at the upper cervical level observed in our study do not lead to abnormalities in intracranial venous flow.

In a second step, we compared our study cohort of MS patients with a cohort of migraine patients, who had been investigated previously.[15] Both patient cohorts and their respective controls have been investigated with precisely the same methodology, including the same MR scanner and identical sequence parameters and analysis algorithms in order to ascertain comparability between the studies. Moreover, both patient cohorts were meticulously matched with controls regarding age and gender. There were no significant differences in quantitative assessments of secondary venous outflow between patients with MS and patients with chronic migraine. However, there was a significant difference between the respective patient groups and their healthy controls. Therefore, the alterations in the venous outflow as assessed with our MR-based methodology are not specific to MS.

The incidence of headaches has been reported to be as high as 55.6% in patients with MS.[26] Gee et al.[26] have reported mid-brain lesions, especially in a periaqueductal

location, to be associated with migraine-type headaches in patients with MS. However, analyzing the images of our migraine patients, we did not identify any structural lesions and specifically, no mid-brain abnormalities. Moreover, none of the migraine patients reported clinical signs suggestive of a demyelinating disorder. We are therefore convinced that the migraine cohort and the MS cohort can be clearly distinguished on the basis of both their clinical history and their structural MRI findings.

A recent ultrasonography study on US veterans with MS found no differences between patients with MS and controls with migraines or healthy controls.[27] This study included 18 MS patients and 11 age-matched controls. These controls were either patients with migraine headaches or individuals without a neurological diagnosis. The authors do not differentiate between the healthy controls and the migraine patients in the analyses and use these 11 individuals as a control population for the MS patients. It is therefore possible that the lack of differences in venous drainage in this study is due to the presence of migraine patients in the control population, which in turn would be in concordance with our MRI results.

In addition to the patients with MS and migraine headaches reported in this manuscript, we have investigated patients with a status after mild traumatic brain injury with the identical MRI protocol including quantitative phase contrast sequences of craniocervical venous outflow (publication currently under review). We observed similar alteration in venous drainage patterns in this patient cohort, which further underlines the presumed non-specificity of the finding for MS.

The mechanism of the increase of drainage via secondary venous outflow in our study remains to be elucidated. Very little is currently known about the regulation of cerebral venous drainage under physiological or pathological conditions. Potential mechanisms for venous outflow alterations might include post-inflammatory changes of the venous vasculature and drainage which could, for example, be mediated by inflammatory cytokines.

In MS, inflammatory changes are known to occur both in lesions and in the normal appearing white matter. This inflammatory response might affect endothelial cells and local production of vasoactive substances, such as nitric oxide (NO) and endothelin. Additional investigations are necessary to elucidate the dynamics of venous vascular changes. Another potential mechanism might relate to an altered texture of the brain, leading to an increased rigidity or stiffness of the parenchyma and thus potentially to altered flow and drainage patterns. Whichever mechanisms are responsible for the observed changes, it is noteworthy that similar alterations were seen in paediatric, adolescent and adult patients, and in patients with short and long duration of disease. This indicates that changes of craniocervical venous drainage occur relatively early during the disease course.

In conclusion, our MR-based study employing cardiac-gated phase-contrast and MR-venographic techniques demonstrated altered secondary venous outflow patterns in patients with MS compared with matched healthy controls. Because similar venous outflow patterns were observed in subjects with chronic migraine, we conclude that the observed alterations are not specific for MS, and therefore unlikely to represent a primary pathogenic mechanism.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

References

1. Khan O and Tselis A. Chronic cerebrospinal venous insufficiency and multiple sclerosis: science or science fiction? *J Neurol Neurosurg Psychiatry* 2011; 82: 355.
2. Filippi M, Rocca MA, Barkhof F, et al. Multiple sclerosis and chronic cerebrospinal venous insufficiency: the neuroimaging perspective. *AJNR Am J Neuroradiol* 2011; 32: 424–427.
3. Wattjes MP, van Oosten BW, de Graaf WL, et al. No association of abnormal cranial venous drainage with multiple sclerosis: a magnetic resonance venography and flow-quantification study. *J Neurol Neurosurg Psychiatry* 2011; 82: 429–435.
4. Zivadinov R, Marr K, Cutter G, et al. Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS. *Neurology* 2011; 77: 138–144.
5. Fox RJ and Rae-Grant A. Chronic cerebrospinal venous insufficiency: Have we found the cause and cure of MS? *Neurology* 2011; 77: 98–100.
6. Zamboni P, Galeotti R, Menegatti E, et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2009; 80: 392–399.
7. Zamboni P, Menegatti E, Galeotti R, et al. The value of cerebral Doppler venous haemodynamics in the assessment of multiple sclerosis. *J Neurol Sci* 2009; 282: 21–27.
8. Zamboni P, Menegatti E, Weinstock-Guttman B, et al. The severity of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis is related to altered cerebrospinal fluid dynamics. *Funct Neurol* 2009; 24: 133–138.
9. Zamboni P, Galeotti R, Menegatti E, et al. A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency. *J Vasc Surg* 2009; 50: 1348-1358 e1341-e1343.
10. Singh AV and Zamboni P. Anomalous venous blood flow and iron deposition in multiple sclerosis. *J Cereb Blood Flow Metab* 2009; 29: 1867–1878.
11. Lee BB, Bergan J, Gloviczki P, et al. Diagnosis and treatment of venous malformations. Consensus document of the International Union of Phlebology (IUP)-2009. *Int Angiol* 2009; 28: 434–451.

12. Khan O, Filippi M, Freedman MS, et al. Chronic cerebrospinal venous insufficiency and multiple sclerosis. *Ann Neurol* 2010; 67: 286–290.
13. Doepp F, Paul F, Valdueza JM, Schmierer K and Schreiber SJ. No cerebrocervical venous congestion in patients with multiple sclerosis. *Ann Neurol* 2010; 68: 173–183.
14. Baracchini C, Perini P, Calabrese M, Causin F, Rinaldi F and Gallo P. No evidence of chronic cerebrospinal venous insufficiency at multiple sclerosis onset. *Ann Neurol* 2011; 69: 90–99.
15. Koerte IK, Schankin CJ, Immler S, et al. Altered cerebrovenous drainage in patients with migraine as assessed by phase-contrast magnetic resonance imaging. *Invest Radiol* 2011; 46: 434–440.
16. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011; 69: 292–302.
17. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia* 2004; 24(Suppl. 1): 9–160.
18. Tain RW, Ertl-Wagner B and Alperin N. Influence of the compliance of the neck arteries and veins on the measurement of intracranial volume change by phase-contrast MRI. *J Magn Reson Imaging* 2009; 30: 878–883.
19. Alperin N and Lee SH. PUBS: pulsatility-based segmentation of lumens conducting non-steady flow. *Magn Reson Med* 2003; 49: 934–944.
20. Wagshul ME, Chen JJ, Egnor MR, McCormack EJ and Roche PE. Amplitude and phase of cerebrospinal fluid pulsations: experimental studies and review of the literature. *J Neurosurg* 2006; 104: 810–819.
21. Royston P and Altman D. Regression using fractional polynomials of continuous covariates. *Appl Stat* 1994; 3: 429–467.
22. Sundstrom P, Wahlin A, Ambarki K, Birgander R, Eklund A and Malm J. Venous and cerebrospinal fluid flow in multiple sclerosis: A case–control study. *Ann Neurol* 2010; 68: 255–259.
23. Zivadinov R, Schirda C, Dwyer MG, et al. Chronic cerebrospinal venous insufficiency and iron deposition on susceptibility-weighted imaging in patients with multiple sclerosis: a pilot case-control study. *Int Angiol* 2010; 29: 158–175.
24. Ge Y, Zohrabian VM, Osa EO, et al. Diminished visibility of cerebral venous vasculature in multiple sclerosis by susceptibility-weighted imaging at 3.0 Tesla. *J Magn Reson Imaging* 2009; 29: 1190–1194.
25. Alperin NJ, Lee SH, Loth F, Raksin PB and Lichtor T. MR-Intracranial pressure (ICP): a method to measure intracranial elastance and pressure noninvasively by means of MR imaging: baboon and human study. *Radiology* 2000; 217: 877–885.
26. Gee JR, Chang J, Dublin AB and Vijayan N. The association of brainstem lesions with migraine-like headache: an imaging study of multiple sclerosis. *Headache* 2005; 45: 670–677.
27. Marder E, Gupta P, Greenberg BM, et al. No cerebral or cervical venous insufficiency in US veterans with multiple sclerosis. *Arch Neurol* 2011.