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**No association of abnormal cranial venous drainage with multiple sclerosis:  
An MR venography and flow-quantification study**

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## **Abstract**

**Background:** Recent studies using color-coded Doppler sonography showed that chronic impaired venous drainage from the central nervous system is almost exclusively found in multiple sclerosis (MS) patients. This study aimed to investigate the intracranial and extracranial venous anatomy and the intracerebral venous flow profile in patients with MS and healthy controls using magnetic resonance venography (MRV). **Methods:** Twenty patients with definite MS and twenty age and gender matched healthy controls were examined. MR imaging was performed on a whole-body 3T MR system including both 3D phase-contrast and dynamic 3D contrast-enhanced MRV as well as flow quantification of the internal cerebral veins and the straight sinus. Image analysis was performed by two experienced interventional neuroradiologists blinded to clinical data and structural brain imaging. The intracranial and extracranial neck veins were analyzed for stenosis/occlusion and alternative venous drainage pattern. **Results:** A completely normal venous anatomy was observed in ten MS patients and twelve controls. Anomalies of the venous system (venous stenosis/occlusions) were found in ten MS patients and eight healthy controls. An anomalous venous system in combination with associated alternative venous drainage was observed in six MS patients and five healthy controls. Flow quantification showed no venous backflow in any MS patient or control. **Conclusions:** Findings suggestive of anomalies of the cranial venous outflow anatomy were frequently observed in both MS patients and healthy controls. Given the normal intracranial venous flow quantification results it is likely that these findings rather reflect anatomical variants of venous drainage than clinically relevant venous outflow obstructions.

## **Introduction**

Multiple sclerosis (MS) is considered to be an immune-mediated disease of the central nervous system (CNS) characterized by inflammation, demyelination and neurodegeneration. The current pathophysiological concept is based on a complex interaction of autoreactive T- and B-cells recognizing myelin antigens of CNS [1,2]. Clinically and radiologically, MS is characterized and defined by clinical symptoms and signs that reflect lesion dissemination in space and in time [3,4].

Recently, the concept of chronic cerebrospinal venous insufficiency (CCSVI) in MS has been postulated. The concept of CCSVI suggests that venous drainage from the CNS is frequently impaired in MS patients but not in healthy controls subjects [5,6]. It has been proposed that chronic venous reflux and hypertension might lead to increased iron deposition in the brain which might lead to subsequent MS pathology including inflammation and neurodegeneration [7,8]. The initial data on CCSVI stems from studies using extracranial color-Doppler (ECD) and transcranial color-coded Doppler sonography (TCCS) showing 288 normal and 257 abnormal findings in MS patients compared to 861 normal and 24 anomalous parameters in healthy controls. One of the criteria defining abnormal cerebrospinal venous drainage was the presence of reflux in the deep cerebral veins. These findings in combination distinguished MS with a sensitivity, specificity, positive and negative predictive values of 100% [5].

Given the major implication of these findings in terms of both MS pathogenesis and treatment concepts, independent research is needed in order to confirm or refute the original findings. A major point of criticism is that the concept of CCSVI is mainly based on ECD and TCCS methods which are strongly operator-dependent and that intracranial venous blood flow is difficult to measure. In contrast, magnetic resonance venography (MRV) is a non-invasive, sensitive, operator-independent technique for the evaluation of venous anatomy and pathologic changes and is widely used in the clinical setting [9,10]. Such an objective imaging technique is also needed in case treatment of a morphological abnormality is contemplated. However, data on MRV in the detection of venous outflow abnormalities suggestive of CCSVI are rather limited.

The aim of our study was to investigate the cerebral and cervical venous outflow anatomy in patients with MS and matched healthy controls with MRV. Using MR flow quantification, the

second aim was to determine whether certain venous drainage patterns might be associated with pathological intracranial venous backflow.

## **Patients and Methods**

### ***Patients***

This study was designed as a comparative cross-sectional in patients with definite MS and age and sex matched healthy control subjects. The study was approved by the institutional review board of the VU University Medical Center Amsterdam and written informed consent was obtained from all participants. Inclusion criteria were: diagnosis of MS according to the revised International Panel criteria, age 18-50 years, ambulant, or healthy volunteer [3]. Exclusion criteria were: history of other immunological and or malignant diseases, pregnancy, contraindication for MRI (e.g. pacemaker), claustrophobia, allergic reactions to gadolinium-based contrast media, impaired renal function. Twenty patients with the diagnosis of MS presenting to our MS outpatient clinic were included. Nineteen patients had a relapsing-remitting and one patient a primary progressive disease course. Additionally, twenty age and gender matched healthy controls were selected. The demographic and clinical characteristics of the study population are given in Table 1.

**Table 1:** Characteristics of MS patients and healthy control subjects

	<b>Patients</b>	<b>Controls</b>
No. subjects (F/M)	20 (15/5)	20 (15/5)
Mean age $\pm$ SD (y)	35.1 $\pm$ 9.0	34.5 $\pm$ 9.2
Mean disease duration $\pm$ SD (y)	8.7 $\pm$ 6.2	-----
Median EDSS (range)	2.25 (0-6)	-----
Disease modifying therapy at time of scan (yes/no)	14/6	-----
Mean treatment duration (months)	37.6	-----

SD: standard deviation

EDSS: Expanded Disability Status Scale

F: female, M: male

y: years

### ***MRI acquisition***

MRI was performed on a whole-body 3T MR system (Signa HDXt, General Electric, Milwaukee, USA) using an 8-channel head coil with a maximum slew rate of 150 mT/m/s and a maximum gradient amplitude of 50 mT/m.

The MRI protocol consisted of a multi-sequence protocol including the following pulse sequences:

- Structural brain imaging: axial 2 dimensional (D) proton-density/T2-weighted fast spin echo (matrix 416x320, field of view (FOV) 25x19 cm<sup>2</sup>, slice thickness: 3.0 mm, repetition time (TR) 4100 ms, echo time (TE) 20/112 ms, echo train length (ETL) 24, numbers of signal averaged (NSA) 2), sagittal 3D fluid-attenuated inversion-recovery (FLAIR) (matrix 224x224, FOV 25x25 cm<sup>2</sup>, slice thickness 1.2 mm, TR 8000 ms, TE 2352 ms, inversion time 124 ms, ETL 230, NSA 1), axial 2D T1-weighted spin echo (matrix: 224x224, FOV 25x19 cm<sup>2</sup>, slice thickness 3.0 mm, TR 580, TE 8 ms, NSA 1) after intravenous administration of contrast media (0.1. mmol/kg/bodyweight Gadobutrol, Gadovist®, Bayer Schering Pharma, Germany). 3D FLAIR images were reformatted into axial orientation (3 mm slice thickness).
- MRV: 3D (Inhance) phase-contrast angiography (FOV: 32x26 cm<sup>2</sup>, slice thickness: 1.4 mm, TR 11.6 ms, TE 4.9 ms, flip angle (FA) 8 degrees, 19 projection images, flow encoding: 15 cm/s). Multi-phase 3D contrast-enhanced MR angiography (matrix: 320x224, FOV 32x24 cm<sup>2</sup>, slice thickness 3.0 mm, TR 4.3 ms, TE 1.4 ms, FA 30 degrees, five dynamic acquisitions). After acquisition, images of all five dynamic acquisitions were subtracted from the base image for each location. The Inhance 3D MRA was sagittally acquired covering the head and neck and reformatted into 18 maximum intensity projections around the CC-axis. The FOV of the phase-contrast angiography included the whole brain and at least the distal half of the neck, the FOV multi-phase 3D contrast-enhanced MR angiography ranged from the aortic arch to the confluens sinuum. Therefore, the crucial area of the skull base and the upper neck (most of the described cases of venous stenosis were located in this area) were depicted by both angiographic methods.
- Phase-contrast flow quantification: a phase-contrast gradient echo sequence was acquired to quantify the flow in the v. interna cerebri and sinus rectus: 2D

acquisition, TR 11.2 ms, TE 4.1 ms, matrix : 448x448, FA : 8 deg., FOV : 26x26 cm<sup>2</sup>, slice thickness 5 mm, cardiac-gated, reconstructed with 30 cardiac phases and 4 views per segment. Velocity encoding: 50 cm/s. The flow quantification was done in two planes perpendicular to the internal cerebral veins and the straight sinus. Postprocessing and analysis of the data was performed on an AW workstation by a rater (physicist, WDG) who was blinded to the structural and angiographic images as well as to the clinical data of the study subjects. Both internal cerebral veins and the sinus rectus were analyzed separately. Flow plots were made and checked for reflux or almost stationary flow (Figure 1).

### ***Image analysis***

As a first step, image annotations and identifiers were removed and replaced by new unique identification numbers. The structural MR images (PD/T2-weighted, FLAIR and T1-weighted images) and angiographic images were stored separately.

All angiographic images were scored by two interventional neuroradiologists (RVDB, JCB) in consensus. Both readers only had access to the angiographic series but not to the structural MR images and were blinded to the demographic (except date of birth) and clinical information of all study subjects.

The following intracranial and extracranial venous structures were analyzed separately for possible abnormalities (aplasia, hypoplasia, stenosis, and occlusion). Extracranial: external jugular veins, internal jugular veins. Intracranial: superior sagittal sinus, inferior sagittal sinus, straight sinus, transverse sinus, sigmoid sinus, great cerebral vein (of Galen), internal cerebral veins. A stenosis was defined as a narrowing of the vessel of at least 50%, an occlusion was defined as no patency of the vein without any flow on both the phase-contrast and contrast-enhanced MRV.

In addition, the entire intracranial and extracranial venous system was scored for alternative venous drainage with or without associated stenosis of certain venous structures. Indicator of alternative drainage pattern also considered venous structures/pathways which were not scored for abnormalities in the first step such as superficial cerebral veins, cortical veins, basal vein (of Rosenthal), vein of Trolard, choroidal veins, thalamostriate (terminal) veins, superior and inferior petrosal sinus, cavernous sinus, occipital sinus, epidural veins, occipital plexus, vertebral plexus, deep cervical veins. Physiologically asymmetric venous drainage

patterns in particular of the transverse and sigmoid sinus were not considered as pathological.

The final conclusive classification of the venous systems in terms of findings suggestive of an anomalous intracranial venous drainage according to our imaging protocol and rating systems was based on the following definition:

*No evidence of anomalous venous anatomy*: normal/physiological venous drainage without evidence of venous stenosis and/or alternative venous drainage.

*Anomalous venous anatomy*: Presence of an extra- and/or intracranial venous stenosis in combination with or without alternative (compensatory collateral) venous drainage.

- *Possibly anomalous venous anatomy*: Presence of an extra- and/or intracranial venous stenosis without alternative venous drainage pattern.
- *Probably anomalous venous anatomy*: Presence of an extra- and/or intracranial venous stenosis in combination with alternative (compensatory collateral) venous drainage.

## **Results**

### ***MRV***

An anomalous venous system was found in ten MS patients compared to eight healthy controls (Table 2). An intracranial and/or extracranial venous stenosis was observed in twelve MS patients and in eight healthy controls; two MS patients showed a combination of an intracranial and extracranial venous stenosis. One MS patient and one healthy control had a bilateral intracranial venous stenosis, four MS patients and three healthy controls showed a bilateral extracranial venous stenosis. Two MS patients showed a combination of a stenosis of the internal and external jugular vein. Figures 2-7 represent examples of normal and anomalous venous outflow anatomy in MS patients and healthy controls.

In those healthy controls presenting with an alternative drainage pattern, the associated venous obstruction was located in the internal jugular vein (two bilateral stenosis, one unilateral stenosis, one occlusion) and in the sigmoid sinus (one subject). The location of venous obstruction in all MS patients with an associated alternative venous drainage was located in the internal jugular vein (bilateral in four patients). The most frequent alternative drainage pattern was a drainage via the occipital, paravertebral and/or cervical venous



plexus or external jugular vein in combination with a venous obstruction located in the internal jugular vein (in all six MS patients and four healthy controls.)

**Table 2:** MR venography results of MS patients and healthy controls

	Patients (n=20)	Controls (n=20)
<b>Intracranial stenosis/occlusion</b>	4	1
Transverse sinus	2	-
Sigmoid sinus	2	1
<b>Extracranial stenosis/occlusion</b>	8	7
Internal jugular vein	8	7
External jugular vein	2	-
<b>Alternative drainage</b>	6	5
<b><u>Final classification</u></b>		
No evidence of abnormal venous anatomy	10	12
Anomalous venous anatomy	10	8
Possible anomalous venous anatomy	4	3
Probably anomalous venous anatomy	6	5

### ***Flow quantification***

Among all study subjects, a total number of 3 veins were only visible on the MRV but not visible on the quantitative flow sequence scan probably due to slow flow: both internal cerebral veins could not be observed in one MS patient and the left internal cerebral vein could not be observed in a healthy control. Overall, venous backflow/reflux could not be observed in a healthy control subject or in any MS patient (Figure 8). In seven veins at some point during the cardiac cycle a near to zero flow velocity was observed when compared to the main velocity. This occurred in two subjects (one MS patient and one healthy control each) in the straight sinus and in other two subjects (one MS patient and one healthy control each) in the left internal cerebral vein. In three other subjects (two MS patients, one healthy control) this flow pattern was observed in the right internal cerebral vein. However, in none of these patients backflow/reflux was observed.

## Discussion

The recently introduced pathophysiological concept of CCSVI in MS patients and its possible implications on MS pathophysiology and treatment has raised great interest in both patient and medical community. So far, this theory is mainly based on ECD and TCCS. Doppler encoded ultrasound is a strongly operator-dependent image modality and not easy to blind in terms of clinical features. In addition, TCCS is strongly dependent on a transcranial insonation window and angle and has a limited resolution. The challenges of ECD and TCCS in terms of the diagnosis of venous outflow obstruction in MS patients is underscored by the fact that the initial findings suggesting the concept of CCSVI could not have not been reproduced by another recent published study [11].

In this study we aimed to investigate the cranial venous outflow anatomy of MS patients as well as age and gender matched healthy control subjects in order to validate the ultrasound based findings of venous outflow obstruction in MS patients. Using MR venography, a sensitive and reproducible imaging modality widely used in the clinical setting, we were not able to reproduce earlier ultrasonographic findings. A classical normal appearance of the intracranial and cervical venous system according to the anatomy textbooks was observed in about 50% of the MS patients and healthy controls. Cases with a possibly or probably anomalous venous outflow anatomy were almost equally distributed between MS patients and healthy controls. Our results are in line with a recently published venous and cerebrospinal fluid flow study including 21 MS patients and 20 healthy controls. The authors did not find any significant differences between MS patients and healthy controls concerning the blood flow in the internal jugular veins and prevalence of reflux in the internal jugular veins [12]. These results underscore that the venous vascular system of the brain and neck is quite complex and that variants of the classical venous anatomy can be observed in a substantial proportion of humans [13-16]. The most important question remains the correct interpretation of these variants in terms of possible pathophysiological relevance, clinical consequences and the necessity of treatment.

In order to address the crucial question whether the observed findings suggestive of venous outflow abnormality effectively leads to a chronic venous backflow as described in Doppler ultrasound studies in MS patients, we performed MR phase contrast flow quantification of the straight sinus and internal cerebral veins. Venous backflow/reflux could not be observed in any of our study participants, including those subjects diagnosed with probably

anomalous cranial venous outflow. Therefore these results do not support the pathophysiological relevance of these alternative venous outflow patterns. In addition, it is unlikely that the anomalous venous anatomy is directly associated with MS symptoms and disease course or even the cause of MS [17]. Even in patients with a real pathological venous outflow anatomy such as cerebral venous thrombosis or radical neck dissection removing jugular veins, higher incidences of MS have not been reported [18]. Taking these facts in into consideration, in our view this should lead to reluctance with respect to therapeutic interventions [19].

It is difficult to directly compare our results with those obtained from previous Doppler ultrasound studies since both methods are based on different techniques with their own advantages and drawbacks. A recently published study on intra-individual comparison between neck MRV, Doppler sonography and selective venography for the diagnosis of CCSVI in MS patients and healthy controls reported a substantial difference between MRV and Doppler ultrasound [20]. However, the crucial question remains which of these diagnostic tests have to be considered as the gold standard. Some authors consider catheter angiography as the gold standard in the detection of cranial venous outflow anatomy. However, regardless of the imaging modality used the crucial question remains whether findings suggestive of venous outflow obstruction reflect a real pathological and pathophysiological relevant conditions or rather an anatomical variant. The work-up of possible venous obstructions requiring treatment would need to focus on identification of morphological lesions – this would require anatomical imaging (catheter angiography or MRV) rather than physiological evaluations (like blood flow measurements with ultrasound). We have to be aware that all available standard imaging approaches for the evaluation of the cranial venous system represent rather a snap-shot. The venous blood flow is influenced by many different physiological factors and their interaction such as respiratory changes, swallowing, central venous pressure, position of the patient (supine, sitting, upright), muscle contraction, etc. Regarding the analysis of the intracranial and cervical venous systems it is almost impossible to take all of these factors into account regardless of the imaging modality used.

A limitation of our study is the limited number of MS patients and healthy controls subjects which limits the possibility to draw definite conclusions. The sample size number was based on the suggested almost absolute difference in presence of venous abnormalities between

MS patients and healthy controls. Nevertheless, the present sample size would allow to find a difference of 50% or more with a power of about 0.8. In addition, our results based on MRV have not been confirmed or refuted by another imaging modality such as Doppler sonography. However, our study represents the largest case-control dataset of MRV in the evaluation cranial venous outflow in MS patients and healthy controls so far. Given the fact that the initial results suggesting that MS is associated with a pathological venous outflow anatomy presented sensitivity, specificity, positive and negative predictive values of 100%, our study population is large enough to refute these data. In addition, a validation of MRV results in this context using MR flow quantification has not been performed yet. However, larger studies using different imaging approaches are necessary to reproduce and validate our data.

In conclusion, our data suggest that the cranial and cervical venous system on MRV is very complex and highly variable in normal healthy controls as well as in MS patients. Findings suggestive of anomalous cranial venous outflow in terms of venous stenosis alone or in combination with alternative venous drainage pattern are equally distributed between MS patients and healthy controls. Given the fact that these findings are not associated with venous backflow based on MR flow quantification, it is more likely that these situations represent rather anatomical variants than pathological conditions that might be causally associated with MS pathology.

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**Statement of competing interests**

The authors report no conflicts of interests.

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### **Legend to the Figures:**

**Figure 1:** Venous blood flow quantification in the straight sinus and internal cerebral veins. Figure right side: Regions of interest were placed on coronal phase-contrast images for quantitative flow measurement in the straight sinus (top) and both internal cerebral veins (bottom). Measurements were performed in planes perpendicular to vessel directions. Figure right side: example of quantitative flow patterns of a healthy control with normal findings for quantitative flow profiles and without any evidence of venous backflow/reflux in the straight sinus (top) and internal cerebral veins (middle and bottom).

### **Figure 2:**

Maximum intensity projection images of the phase-contrast (left, middle) and contrast-enhanced (right) MRV obtained from a healthy control. Intracranial and cervical venous anatomy was classified as normal without any evidence of venous stenosis and/or alternative venous drainage.

### **Figure 3:**

Maximum intensity projection images of the phase-contrast (left, middle) and contrast-enhanced (right) MRV of 44-year-old MS patient. The intracranial and cervical venous anatomy was classified as normal without evidence of venous stenosis and/or alternative venous drainage. Please note the prominent deep cervical vein (arrow) without any signs of congestion which was considered as a normal anatomical variant.

### **Figure 4:**

Maximum intensity projection images of the phase-contrast (left, middle) and contrast-enhanced (right) MRV 25-year-old MS patient with a bilateral stenosis (arrows) of the internal jugular vein which could be easily identified on the phase-contrast MRV. In particular, the contrast-enhanced MRV showed a prominent cervical and occipital venous drainage pattern including the occipital vein and external jugular vein (arrows) with signs of congestion. In addition a prominent occipital could be identified on the right side.



**Figure 5:**

Maximum intensity projection images of the phase-contrast (left, middle) and contrast-enhanced (right) MRV 47-year-old healthy control with a persistent bilateral stenosis of the internal jugular vein (closed head arrows) and a dilatation and congested appearance of the cervical and occipital venous drainage system (open head arrows) including the occipital vein and external jugular vein.

**Figure 6:**

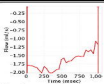
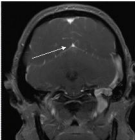
Maximum intensity projection images of the phase-contrast (left) and contrast-enhanced (middle) MRV showing a stenosis of the right sigmoid sinus (arrows) of a 35-year-old MS patient without any signs of associated abnormal (collateral) drainage. This stenosis could also be identified on the source images of the contrast-enhanced MRV (right).

**Figure 7:**

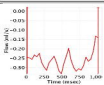
Maximum intensity projection images of the phase-contrast MRV of a 27-year old healthy control with a bilateral stenosis of the internal jugular veins (arrows) without any signs associated abnormal (collateral) venous drainage. In particular, no dilatation and congestion on the cervical and occipital venous drainage pathway could be observed.

**Figure 8:**

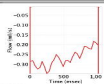
Examples of quantitative venous blood flow analysis in the straight sinus (top row) and internal cerebral veins (middle and bottom row) of healthy controls (HC) and MS patients who were classified as having a normal (left columns), possibly anomalous (middle columns) and probably anomalous (right columns) venous outflow anatomy. A venous backflow/reflux could not be observed in any MS patient nor healthy control.



Flow 1



Flow 2



Flow 3

