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FULL PAPER

Lack of correlation between extracranial venous abnormalities and multiple sclerosis: a quantitative MRI study

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Objective: We aimed to evaluate the presence of venous stenosis and blood flow abnormalities in the neck vessels of patients with multiple sclerosis (MS), in respect to a group of age- and sex-matched healthy controls (HC), and their possible relations with clinical variables using a semi-automated quantitative MRI method.

Methods: 45 patients with relapsing remitting MS and 40 HC were enrolled in this study. Flow rates and cross-sectional areas of arterial and venous neck vessels were assessed by phase-contrast MRI at two different neck levels (C2–C3 and C6–C7), and differences between groups were evaluated with an unpaired *t*-test. Correlation between blood flow variables and clinical parameters was analyzed with Spearman's test.

Results: A significant internal jugular vein (IJV) stenosis was found in 23/45 (51.1%) patients with MS and 18/40 (45.0%) HC. No differences were observed between

patients with MS and HC for any of the flow measures obtained. No correlations were found between MRI measures and any of the tested clinical variables.

Conclusion: No differences in the IJV area emerged at quantitative MRI evaluation, suggesting that stenosis of the extracranial veins is unrelated to MS. Furthermore, no flow differences in the neck vessels were found between patients with MS and HC in any of the tested flow measures, with no correlation with clinical variables. Our results confirm that the hypothesis of the presence of extracranial venous abnormalities in MS, both in terms of stenosis or flow measures, is not suitable.

Advances in knowledge: Neck venous drainage abnormalities have been claimed to be associated with MS. Conversely, our quantitative MRI analysis seems to exclude that extracranial venous alterations are related to the disease.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory neurodegenerative disease of the central nervous system characterized by demyelination and axonal loss.¹ To date, although environmental and genetic factors are considered to play a key role in the development of MS, the main causes that start the pathology are still unknown.²

Among the potential factors that were related to MS, abnormal venous haemodynamics in the neck, including

venous reflux and stenosis, has been hypothesized to be a feature of MS.^{3–6}

During the past few years, different studies were carried out to investigate the possible role of extracranial venous flow abnormalities in MS. These studies used different image modalities such as ultrasound^{3,5,7–14} and MRI, including contrast-enhanced MR venography (CE-MRV), phase-contrast MRI or time-of-flight sequences,^{4,15–20} and a combination of different imaging modalities.^{21–26} These studies, however, yielded somewhat conflicting results, and

the role of venous abnormalities in MS still remains in discussion.

To the best of our knowledge, only few studies investigated possible extracranial venous abnormalities using a quantitative MRI method, comparing patients with MS and healthy controls (HC), with conflicting results.^{15,16,18,19,25} Furthermore, to date, no studies were performed to investigate the possible relationships between venous flow abnormalities, internal jugular vein (IJV) stenosis and clinical outcomes. Thus, the aim of the present study was to perform a functional and anatomical evaluation of neck veins in patients with MS compared with a group of HC, correlating MRI flow measures and clinical variables, in order to elucidate a possible role of venous abnormalities in MS.

METHODS AND MATERIALS

Study design

Our purpose was to evaluate whether any differences occur in terms of venous flow measures between patients with MS and HC. Furthermore, we aimed to evaluate the incidence of IJV stenosis in both groups. To take the possible role of IJV stenosis into account, we split our population into patients with stenotic MS and stenotic HC and tested whether there was any difference between the venous flow measures when considering an anatomical condition that could alter the flow pattern in both groups. Finally, possible correlations between flow measures and clinical variables were tested, considering both the whole MS group and only the stenotic MS subgroup.

Subjects

45 patients with relapsing remitting multiple sclerosis (RR-MS) and 40 HC were enrolled in the study. Only patients fulfilling the criteria for MS diagnosis according to McDonald et al²⁷ were included in the analysis. HC had no history of neurological disorders or any other pathological condition that could affect the CNS or the intracranial/extracranial blood flow. Demographic information of all subjects included in the study is listed in Table 1.

The local ethics committee approved the study and the written informed consent form was signed by all subjects. Expert neurologists assessed the clinical variables for each patient with MS within 1 week from the MRI scan. These included, along with disease duration, measured from the first occurrence of

symptoms clearly related to the disease, the following variables: expanded disability status scale, annualized relapse rate, multiple sclerosis severity score and number of relapses.

MRI data acquisition

MR acquisitions were performed on a 3.0-T scanner (Trio; Siemens Medical Systems, Erlangen, Germany) with a volume transmitter coil and a 12-channel head-neck receiver coil. During the MR acquisition, the subjects were lying supine, with the head fixed by straps and foam pads in order to minimize possible head movements.

The acquisition protocol included phase-contrast MRI [repetition time (TR) = 66.8 ms; echo time (TE) = 5.3 ms; voxel size: $0.5 \times 0.5 \times 3.0 \text{ mm}^3$; single slice in an axial orientation; 30 time points] with peripheral retrospective triggering, acquired at two different cervical levels [an upper level, around C2 (C2–C3), and a lower level, around C6 (C6–C7), according to previous studies^{4,16,17,19}], and with a maximum encoding velocity (VENC) of 50 cm s^{-1} ; a three-dimensional fluid-attenuated inversion recovery sequence (TR = 6000 ms; TE = 396 ms; inversion time = 2200 ms; flip angle = 120° ; voxel size = $1 \times 1 \times 1 \text{ mm}^3$; number of slices = 160; sagittal orientation) covering the whole brain, for the visual assessment of the demyelinating lesions; and a three-dimensional CE-MRV sequence (volumetric interpolated brain examination; TR = 3.97 ms; TE = 1.68 ms; voxel size: $1 \times 1 \times 1 \text{ mm}^3$; sagittal orientation) acquired before and after the i.v. administration of gadolinium-based contrast agent, used for the anatomical assessment of neck veins.

All sequences used for the analysis were chosen according to the recently published guidelines of the International Society of Neurovascular Disorders²⁸ for the correct assessment of detection of extracranial venous abnormalities.

MRI data analysis

For all vessels, quantitative analyses were carried out using a dedicated software [Signal Processing in NMR (SPIN); Detroit, MI] and all the processing steps, along with the choice of the corresponding flow measures, were derived from previous literature.^{4,16,17,19}

For quantitative flow measures, the contour of the vessels in the axial plane was manually hand-drawn using both the magnitude

Table 1. Subject demographics and clinical variables

Clinical variable	HC	MS
Age (mean $\pm$ SD) (years)	39.9 $\pm$ 13.8 (range 21–65)	39.0 $\pm$ 10.0 (range 24–65)
Sex (M/F)	22/18	18/27
DD (mean $\pm$ SD) (years)	n.a.	10.5 $\pm$ 7.4 (range 1–30)
Number of relapses (median)	n.a.	4 (range 1–21)
EDSS (median)	n.a.	3.0 (range 1.5–6.0)
ARR (median)	n.a.	0.48 (range 0.13–3.68)
MSSS (median)	n.a.	4.35 (range 1.66–8.64)

ARR, annualized relapse rate; DD, disease duration; EDSS, expanded disability status scale; F, female; HC, healthy controls; M, male; MS, multiple sclerosis; MSSS, multiple sclerosis severity score; n.a., not applicable; SD, standard deviation.

and phase images as input. Segmented vessels included in the analysis, were, bilaterally: common carotid arteries, internal carotid artery, external carotid artery, vertebral arteries, vertebral veins, IJV and external jugular veins, depending on the cervical level. Other major veins, including the deep cervical veins, common facial veins or anterior facial veins, were included when observed. For major arteries and IJVs, phase aliasing could occur during systole; such phase aliasing was corrected using a phase-unwrapping algorithm.⁴

The unwrapped phase $\phi(\vec{r})$ was then used to derive voxelwise an estimate of the blood velocity according to:

$$v(\vec{r}) = \frac{\phi(\vec{r})}{\pi} VENC$$

For a given vessel of section Ω , the flow was then computed as:

$$Q_{\Omega} = \int_{\Omega} v(\vec{r}) d\Omega$$

For all vessels, the mean average velocity, volume flow rate (average, positive and negative) and total flow volume were obtained. Volume flow rate curves were inspected on a case-by-case basis to identify abnormal flow patterns. From the above-mentioned parameters, derived measurements were also computed. These included: the total arterial flow rate (tAF) and the total venous flow rate, defined as the sum of the flow rates of all considered arteries and veins, respectively; the normalized internal jugular vein flow rate, calculated as the ratio between the IJV flow rate and the tAF; the arteriovenous mismatch (AV-mismatch), obtained as the difference between tAF and total venous flow rate, normalized to tAF; and the ratio between subdominant and dominant IJV flow rates [calculated as the minimum of the left internal jugular vein (L-IJV) or right internal jugular vein (R-IJV) flow rates], both at C2–C3 and C6–C7 levels (ratio between subdominant internal jugular vein flow rate and dominant internal jugular vein flow rate).

On CE-MRV, two expert neuroradiologists performed in consensus the anatomic assessment of the IJVs for the identification of stenosis, aplasia and atresia. Based on previous studies,^{4,17} stenosis was defined as an IJV showing a cross-sectional area (CSA) $<25 \text{ mm}^2$ (roughly one-third of the CSA for an average IJV diameter of 1 cm, assuming a circular shape) at the C6–C7 level. For the C2–C3 level, an IJV showing a CSA $<12.5 \text{ mm}^2$ was considered stenotic. IJV atresia was defined as the presence of a clear and abrupt ending in the IJV course from the sigmoid sinus to the confluence with the subclavian vein. Finally, IJV aplasia was defined as the definite and complete absence of an IJV at any of the neck levels. Subjects showing at least one of these structural abnormalities were classified as stenotic.

Statistical analysis

All statistical analyses were performed using Statistical Package for Social Science (SPSS) (SPSS Inc, v. 20.0, Chicago, Ill). Continuous data are reported as mean and standard deviation or as median and range when appropriate. Categorical data are

reported as percentages. The unpaired *t*-test was used for the comparison of continuous data between the MS and control groups. The χ^2 test was used to determine the differences between categories. The Spearman's rank correlation was used to verify whether variables were associated. $p = 0.05$ was set to indicate a statistically significant difference.

RESULTS

The MS and HC groups were not significantly different for age and gender (Table 1).

When evaluating the incidence of IJV structural abnormalities, 23/45 (51.1%) patients with MS and 18/40 (45.0%) HC were classified as stenotic. In particular, 15/45 (33.3%) patients with MS and 12/40 (30.0%) HC showed a significant IJV stenosis, while 8/45 (17.8%) patients with MS and 6/40 (15.0%) HC showed atresia. No aplasia of the IJV was detected in the patients with MS and HC (Figure 1).

Patients with MS and HC did not show significant differences for any of the tested flow variables. In particular, no differences emerged in terms of absolute IJV flow rates, normalized internal jugular vein flow rates, AV-mismatch and the ratio between subdominant internal jugular vein flow rate and dominant internal jugular vein flow rate, both at C2–C3 and C6–C7 levels (Table 2).

When considering only the stenotic subgroups (stenotic-MS and stenotic-HC), again no significant differences were found for age and gender (Table 3).

Also, statistical analysis between stenotic-MS and stenotic-HC did not show any significant differences for any of the calculated flow variables (Table 4).

Finally, when testing for possible correlations between clinical variables and flow parameters, no significant results were observed, when considering either the entire MS sample or only the stenotic-MS subgroup.

DISCUSSION

Our study provides an accurate evaluation of venous haemodynamics in the neck in patients with MS compared with a group of HC, correlating for the first time MRI anatomical and flow parameters with clinical variables. We found no evidence suggesting the presence of neck blood flow abnormalities in MS, and we also demonstrated that IJV stenosis is not associated with the disease, this being a common feature in HC also. Finally, no correlation with any of the tested clinical variables emerged in our sample.

Venous structures, owing to their anatomical properties, show a high intersubject variability,¹⁵ even depending on the body position in which these structures are studied.¹¹ The presence of venous flow abnormalities in MS has been widely investigated during the last years. In particular, most of these studies evaluated the presence of these modifications by means of ultrasound examination.^{3,5,7–14} Obviously, we could not perform any direct comparison with previous ultrasound studies, as these two imaging techniques rely on intrinsic (e.g. user-dependent

Figure 1. Coronal maximum intensity projections of three-dimensional contrast-enhanced MR venography images of the neck vessels of four different subjects, showing various degrees of internal jugular vein (IJV) stenosis: (a) a 44-year-old female healthy control (HC), with no significant stenosis of both IJVs; (b) a 46-year-old female patient with multiple sclerosis (MS), with no significant stenosis of both IJVs; (c) a 32-year-old male HC, with significant stenosis of the left IJV; and (d) a 35-year-old male patient with MS, with significant stenosis of the left IJV.

ultrasound evaluation of flows) and study-dependent (orthostatic evaluation in ultrasound examination) methodological differences. We therefore focused on the direct comparison with previous studies with similar imaging modalities.

Our first result is the comparable incidence of IJV stenosis in MS and HC. To correctly define stenosis in IJV, as reported in previous MRI studies,^{4,16,17,19} we classified as stenotic a subject showing a reduction in the IJV area of, at least, $<12.5 \text{ mm}^2$ (at the C2–C3 level) or $<25.0 \text{ mm}^2$ (at the C6–C7 level). In our sample, according to this classification, 23/45 (51.1%) patients

with RR-MS were classified as stenotic; however, 18/40 (45.0%) HC also proved to have a significant IJV stenosis at C2–C3 or C6–C7 levels. These results are in line with previous findings of high variability of incidence of IJV stenosis on MS and, in particular, in HC.^{8,9,21,26} Our results confirm that the occurrence of IJV stenosis in MS is not common enough to be defined as a feature of the disease; in addition, the high incidence of IJV stenosis in HC confirms that stenosis is related to a physiological variability rather than to a pathological condition. As a further validation of our result, a recent study²⁹ investigating the prevalence of incidental superior IJV narrowing in patients imaged

Table 2. Results of the statistical analysis for flow measures from the healthy controls (HC) vs patients with multiple sclerosis (MS) comparison

Flow variable	HC	MS	<i>p</i> -value
C2 IJV flow rate (mean $\pm$ SD)	8.08 $\pm$ 3.03	7.93 $\pm$ 3.04	0.99
C6 IJV flow rate (mean $\pm$ SD)	11.08 $\pm$ 3.33	10.21 $\pm$ 3.47	0.32
C2 nIJV flow rate (mean $\pm$ SD)	53.9% $\pm$ 17.7%	59.4% $\pm$ 20.8%	0.12
C6 nIJV flow rate (mean $\pm$ SD)	69.0% $\pm$ 18.0%	69.1% $\pm$ 19.6%	0.81
C2 AV-mismatch (mean $\pm$ SD)	2.49 $\pm$ 8.29	2.47 $\pm$ 9.10	0.90
C6 AV-mismatch (mean $\pm$ SD)	−4.00 $\pm$ 9.58	−1.36 $\pm$ 9.15	0.26
C2 sdIJVF/dIJVF (mean $\pm$ SD)	11.39 $\pm$ 27.86	0.93 $\pm$ 43.66	0.20
C6 sdIJVF/dIJVF (mean $\pm$ SD)	3.53 $\pm$ 5.92	5.21 $\pm$ 11.90	0.33

AV-mismatch, arteriovenous mismatch; dIJVF, dominant internal jugular vein flow rate; IJV, internal jugular vein; nIJV, normalized internal jugular vein; SD, standard deviation; sdIJVF, subdominant internal jugular vein flow rate.

C2 IJV flow rate, absolute IJV flow rate at C2–C3 level; C6 IJV flow rate, absolute IJV flow rate at C6–C7 level; C2 nIJV flow rate, nIJV flow rate at C2–C3 level; C6 nIJV flow rate, nIJV flow rate at C6–C7 level; C2 AV-mismatch, AV-mismatch at C2–C3 level; C6 AV-mismatch, AV-mismatch at C6–C7 level; C2 sdIJVF/dIJVF, ratio between sdIJVF and dIJVF at C2–C3 level; C6 sdIJVF/dIJVF, ratio between sdIJVF and dIJVF at C6–C7 level.

Flow rates are expressed in millilitre per second and normalized flow rates are expressed in %.

AV-mismatch and ratios between subdominant and dominant IJV flow rates are adimensional numbers.

p-values were obtained from Student's *t*-test.

Table 3. Subject demographics and clinical variables of the stenotic subgroups

Clinical variable	Stenotic-HC	Stenotic-MS
Age (mean $\pm$ SD) (years)	42.3 $\pm$ 14.2 (range 21–64)	36.5 $\pm$ 8.4 (range 24–51)
Sex (M/F)	15/3	14/9
DD (mean $\pm$ SD) (years)	n.a.	9.4 $\pm$ 7.1 (range 1–30)
Number of relapses (median)	n.a.	4 (range 1–21)
EDSS (median)	n.a.	3.5 (range 2–6.0)
ARR (median)	n.a.	0.59 (range 0.13–3.68)
MSSS (median)	n.a.	5.36 (range 2.03–8.64)

ARR, annualized relapse rate; DD, disease duration; EDSS, expanded disability status scale; F, female; HC, healthy controls; M, male; MS, multiple sclerosis; MSSS, multiple sclerosis severity score; n.a., not applicable; SD, standard deviation.

Stenotic-HC, HC showing a significant anatomical internal jugular vein (IJV) abnormality; Stenotic-MS, patients with MS showing a significant anatomical IJV abnormality.

with neck CT angiography for reasons unrelated to IJV pathology or MS found that 98 (59.8%) out of 164 patients showed absent, pinpoint or flattened IJV in subjects not affected by MS, in line with our results obtained in the group of HC (45.0%).

Our second result is the evaluation, obtained by a quantitative, reproducible and semi-automated method, of neck blood flow abnormalities in MS. We first investigated whether any difference was present between MS and HC in terms of IJV flow (both absolute and normalized), AV-mismatch and asymmetry between dominant and subdominant IJV drainage.

To increase reproducibility, we decided to replicate methods that were adopted in previous MRI studies,^{4,16,17,19} both in terms of definition of stenosis (as previously discussed) and processing of flow measures. In particular, we chose a VENC value of 50 cm s⁻¹, similar to previous studies,⁴ because a smaller VENC value allows a better signal-to-noise ratio. However, phase aliasing for fast blood

flow that could exceed the VENC value is possible. For this reason, a phase-unwrapping algorithm was used to remove the phase aliasing for velocities exceeding the VENC value.

We found no mismatch between arterial and venous flow rates, as no differences were found in terms of AV-mismatch at C2 and C6 levels. In addition, no significant differences occurred in terms of absolute and normalized IJV flow, suggesting that both the absolute IJV flow rate and the percentage of blood flow drained by IJVs in respect to tAF are not altered in the disease. Finally, no influences of IJV flow asymmetry were appreciated, as the IJV subdominant/dominant ratios at the two neck levels were not significant different between the two groups.

We also split our groups into two subgroups according to the presence of IJV stenosis to identify whether this may explain differences in terms of venous flow. We found no significant differences for any of the tested flow variables, neither in the

Table 4. Results of the statistical analysis for flow measures from the comparison between stenotic healthy controls (HC) vs stenotic multiple sclerosis (MS) patients

Flow variable	Stenotic-HC	Stenotic-MS	<i>p</i> -value
C2 IJV flow rate (mean $\pm$ SD)	6.36 $\pm$ 3.04	7.40 $\pm$ 3.38	0.31
C6 IJV flow rate (mean $\pm$ SD)	9.89 $\pm$ 3.90	9.79 $\pm$ 3.97	0.94
C2 nIJV flow rate (mean $\pm$ SD)	43.0% $\pm$ 18.1%	53.6% $\pm$ 23.1%	0.11
C6 nIJV flow rate (mean $\pm$ SD)	59.9% $\pm$ 20.1%	65.4% $\pm$ 23.5%	0.43
C2 AV-mismatch (mean $\pm$ SD)	2.30 $\pm$ 8.43	2.63 $\pm$ 7.27	0.89
C6 AV-mismatch (mean $\pm$ SD)	-1.17 $\pm$ 10.30	-1.89 $\pm$ 9.50	0.82
C2 sdIJVF/dIJVF (mean $\pm$ SD)	15.81 $\pm$ 28.53	-1.42 $\pm$ 64.04	0.29
C6 sdIJVF/dIJVF (mean $\pm$ SD)	3.43 $\pm$ 6.18	7.94 $\pm$ 16.36	0.24

AV-mismatch, arteriovenous mismatch; dIJVF, dominant internal jugular vein flow rate; IJV, internal jugular vein; nIJV, normalized internal jugular vein; SD, standard deviation; sdIJVF, subdominant internal jugular vein flow rate.

Stenotic-HC, healthy controls showing a significant anatomical IJV abnormality; stenotic-MS, patients with MS showing a significant anatomical IJV abnormality; C2 IJV flow rate, absolute IJV flow rate at C2–C3 level; C6 IJV flow rate, absolute IJV flow rate at C6–C7 level; C2 nIJV flow rate, nIJV flow rate at C2–C3 level; C6 nIJV flow rate, nIJV flow rate at C6–C7 level; C2 AV-mismatch, AV-mismatch at C2–C3 level; C6 AV-mismatch, AV-mismatch at C6–C7 level; C2 sdIJVF/dIJVF, ratio between sdIJVF and dIJVF at C2–C3 level; C6 sdIJVF/dIJVF, ratio between sdIJVF and dIJVF at C6–C7 level.

Flow rates are expressed in millilitre per second and normalized flow rates are expressed in %.

AV-mismatch and ratios between subdominant and dominant IJV flow rates are adimensional numbers.

p-values were obtained from Student's *t*-test.

comparison between the whole MS and HC groups, nor in the comparison between stenotic-MS and stenotic-HC subgroups.

Our results, when comparing patients with MS and HC without taking into account the possible effect of stenosis, are in line with most,^{15,18,20,30} but not all,¹⁹ previous studies. A possible explanation for this discrepancy may be the inclusion of patients with MS with progressive subtypes in the study by Sethi et al.¹⁹ Indeed, Feng et al¹⁶ showed that the tAF of progressive forms were different from the tAF observed in RR-MS; thus, the normalization of IJV flows to tAF, which is different between the two subgroups, could explain this discrepancy. Furthermore, it should be noted that in the study by Sethi et al,¹⁹ flow differences emerged when comparing stenotic-MS with the entire HC group (in which 77% of the subjects did not show IJV stenosis), raising the possibility that the large difference in stenosis percentage, rather than the MS condition, may account for some of the flow differences observed. However, further studies with a direct comparison between RR-MS and progressive subtypes should be performed, in order to elucidate possible differences in flow rates between these forms.

Previous studies have investigated the possible differences between stenotic-MS and non-stenotic-MS. Here, we expand this knowledge, including in the analysis, along with a group of HC, a comparison between stenotic-MS and stenotic-HC. Even when comparing these two subgroups, flow parameters did not show any differences, thus allowing us to state that although venous stenosis may well occur in MS, this does not lead to functional modifications in terms of IJV flow rate, IJV flow asymmetry or AV-mismatch. We therefore suggest that to evaluate possible physiopathological abnormalities in MS, the functional information (in terms of blood flow evaluation or microvascular

changes) should be studied, rather than the anatomical information about the presence of IJV stenosis, which is present in a large number of HC also. All these results, taken together, seem coherent with a hypothesis of no role for extracranial blood flows or stenoses in the aetiopathology of MS.

Finally, for the first time, we correlate MR flow measures with clinical variables. Our results showed that flow parameters do not correlate with any of the tested clinical outcomes. This finding, although expected, allows us to confirm that flow abnormalities should not be used as a biomarker of the disease. However, in order to definitely assess the role of flow abnormalities in MS, longitudinal studies, possibly in a larger scale group, should be performed, testing the correlation of modifications in venous flow with clinical impairment.

In conclusion, our findings confirm that venous flow abnormalities are not present in MS and that stenosis is not a feature of the disease, owing to its high incidence in HC also. Finally, no correlation with any of the tested clinical variables emerged, allowing us to disprove the hypothesis of extracranial drainage abnormalities in MS. To fully elucidate possible differences in various phases of MS, further studies should be performed, including progressive MS subtypes with a longitudinal design, possibly also aiming to evaluate microscopic vascular alterations.

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