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RESEARCH ARTICLE

Abnormal venous postural control: multiple sclerosis-specific change related to gray matter pathology or age-related neurodegenerative phenomena?

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Abstract

Background Autonomic nervous system dysfunction has been previously observed in multiple sclerosis (MS) patients.
Objective To assess associations between magnetic resonance imaging-detected neuroinflammatory and neurodegenerative pathology and postural venous flow changes indicative of autonomic nervous system function.
Methods We used a standardized 3T magnetic resonance imaging protocol to scan 138 patients with MS and 49 healthy controls. Lesion volume and brain volumes were assessed. The cerebral venous flow (CVF) was examined by color-Doppler sonography in supine and upright positions and the difference was calculated as ΔCVF. Based on ΔCVF, subjects were split into absolute or quartile groups. Student's *t* test, χ^2-test, and analysis of covariance adjusted for age and sex were used accordingly. Benjamini-Hochberg procedure corrected the *p*-values for multiple comparisons.
Results No differences were found between healthy controls and patients with MS in both supine and upright Doppler-derived CVF, nor in prevalence of abnormal postural venous control. Patients with absolute negative ΔCVF had higher disability scores ($p=0.013$), lower gray matter ($p=0.039$) and cortical ($p=0.044$) volumes. The negative ΔCVF MS group also showed numerically worse bladder/bowel function when compared to the positive ΔCVF (2.3 vs. 1.5, $p=0.052$). Similarly, the lowest quartile ΔCVF MS group had higher T1-lesion volumes ($p=0.033$), T2-lesion volumes ($p=0.032$), and lower deep gray matter ($p=0.043$) and thalamus ($p=0.033$) volumes when compared to those with higher ΔCVF quartiles.
Conclusion No difference in postural venous outflow between patients with MS and healthy controls was found. However, when the abnormal ΔCVF is present within the MS population, it may be associated with more inflammatory and neurodegenerative pathology. Further studies should explore whether the orthostatic venous changes are an aging or an MS-related phenomenon and if the etiology is due to impaired autonomic nervous system functioning.

Keywords MRI · Multiple sclerosis · ANS · Brain atrophy · Inflammation · Venous flow

Introduction

Multiple sclerosis (MS) is a chronic autoimmune-mediated demyelinating disorder of the central nervous system [1]. However, a neurodegenerative component is being increasingly recognized as an important contributor to the disease's pathophysiology [1]. Global and regional brain atrophy in MS have been previously associated with both physical and cognitive decline [2, 3]. One commonly overlooked pathology within patients with MS is impairment of the autonomic nervous system. The level of autonomic impairment in MS has been associated with clinical measures of disability, such as Expanded Disability Status Scale score, and the measures of cervical spinal cord damage, such as cross-sectional area

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[4]. High prevalence of patients with MS who present with various levels of autonomic impairment (45–84%), including cardiovascular, bladder and bowel, sexual and thermoregulatory dysfunction, further corroborate the extensive involvement of autonomic dysfunction in MS [5]. Therefore, a potential link between autonomic dysfunction and both axonal loss and neurodegeneration, which is more prominent in progressive stages of the disease, can be hypothesized.

Studies have shown that a large proportion of patients within the early stages of MS present with autonomic dysfunction, associated with changes in the heart rate variability and lower catecholamine response profiles [6]. In addition to the central vascular autonomic control, questionnaire-based and sudomotor function testing, which include sympathetic skin response, thermoregulatory sweat testing, and quantitate sudomotor axon reflex testing, may provide better supplementary information on autonomic function [7, 8]. Investigating abnormalities of postural cerebral blood flow changes can potentially provide additional insights into the complex neurodegenerative MS pathophysiology.

Previous reports of differential arterial inflow and venous outflow patterns during changes of body position in patients with MS have found a high prevalence of abnormal postural control and potentially implied an autonomic dysfunction [9–11]. Moreover, these reports showed that the prevalence of the impairment was higher in progressive patients compared to those with early MS or patients with other neurological diseases [10, 12]. The internal jugular veins are the main venous drainage pathway for the brain in the supine position, whereas in the upright position, the jugulars collapse and the flow shifts to the vertebral veins and the vertebral venous plexus [13–15]. The reduction of the size and the flow of internal jugular veins in the upright position occurs as a physiological response to opposing gravitational forces, and it allows maintenance of normal cerebral perfusion, resulting in a prevention of excessive orthostatic drainage.

A number of imaging studies have confirmed that the pathways of autonomic control involve the insular, anterior cingulate, and infralimbic cortices [16]. Functional MRI studies were able to demonstrate topographical organization of the autonomic signals associated to the right anterior insula, and have shown that the insular cortex is responsible for parasympathetic activity [17]. Similarly, classic autonomic challenges such as the Valsalva maneuver differentially recruit sympathetic and parasympathetic responses and demonstrate differential lateralization patterns within the anterior and posterior insular cortex [18]. The frontoinsular and cingulate cortex are the fundamental regions responsible for maintaining sufficient basal autonomic control [19]. Since widespread cortical networks include pathways responsible for the autonomic control, MS-associated cortical damage may potentially cause autonomic dysfunction and impaired autonomic hemostasis.

The aim of this study was to assess the prevalence of abnormal postural venous control in both patients with MS and in healthy controls, and to compare the findings with those in the literature. Additionally, our goal was to employ MRI-derived outcomes in order to understand better the association between abnormal postural venous control and inflammatory and neurodegenerative MS pathology.

Materials and methods

Subjects

All participants utilized for this study were part of a cardiovascular, environmental, and genetic study in MS (CEG-MS) [20, 21]. The inclusion criteria consisted of (1) age between 18 and 75 years old; (2) having MRI and Doppler scans completed within 30 days of the clinical examination; (3) MS diagnosis as defined by the 2017-revised McDonald criteria or being a healthy control without any current or prior neurological diseases [22]. The exclusion criteria included: (1) nursing mother or pregnant woman; (2) the presence of a clinical relapse; and/or (3) steroid treatment within 30 days of the MRI scan. The demographic and clinical information was collected by structured questionnaires, physical examination, and by further cross-reference with medical records. Due to the small number of secondary-progressive and primary-progressive MS patients, these were grouped into a single progressive MS group. In order to determine the level of physical disability of patients with MS, an Expanded Disability Status Scale examination was performed by a neurologist. The bladder and bowel functional scores were also used. The study was approved by the local Institutional Review Board and all participants signed a consent form prior to their participation.

MRI acquisition and analysis

MRI scans were obtained using a 3T GE Signa Excite HD 12 Twin Speed 8-channel scanner (General Electric, Milwaukee, WI, USA) with an 8-channel head and neck coil. MRI sequences consisted of an axial 3D-spoiled-gradient recalled T1 weighted image, dual fast spin-echo T2/proton density, and 2D fluid attenuated inversion recovery. A more detailed description of the MRI acquisition protocol was previously published [23].

T1 and T2 lesion volume were obtained by a semi-automated edge detection and contouring/thresholding technique [2]. The normalized volumes of whole brain, gray matter, white matter, ventricular cerebrospinal fluid, and cortex were obtained utilizing SIENAX software (version 2.6) [24]. Regional tissue-specific normalized volumes of the total deep gray matter and the thalamus were derived using

FIRST [25]. In order to reduce the impact of T1 hypointensities, lesions were filled prior to the tissue segmentation [26].

Doppler sonography assessment

Extra-cranial neck vessel examination was performed using an echo-color Doppler (ECD Esaote—Biosound My Lab 25 Gold, Genoa, Italy) equipped with a 7.5–10 MHz transducer. During the procedure, patients were seated on an automated reclining chair that allowed positioning in supine (0°) and upright (90°) positions. A 3-min break between repositionings of the patient allowed redistribution of the venous flow. The examination was performed by a blinded technologist who used a standardized scanning protocol [27]. The blood flow within the jugular and vertebral veins was assessed in both supine and upright positions using manual flow calculations. Time average velocity (V_{MT}) was calculated using a manual correction of the Doppler angle, while manually drawn cross-sectional area measurement was performed on color Doppler settings (Eq. 1). The sites for cross-sectional area measurement were just above the entry of the facial vein (J3) for the jugular veins and at the cervical level of C3–C4 for the vertebral veins. The CVF was calculated by multiplying the V_{MT} over 4 s time phase and the manually drawn cross-sectional area on axial view (Eq. 2).

$$V_{MT} = \Sigma \mathrm{Vi} \times \Delta T \quad (1)$$

$$\mathrm{Flow} = V_{MT} \times \mathrm{CSA} \quad (2)$$

The total CVF in both supine and upright positions was calculated by adding the individual flow of bilateral internal jugular veins and bilateral vertebral veins (Eq. 3). Furthermore, for examining the postural changes within the CVF (ΔCVF), the upright CVF was subtracted from the supine CVF (Eq. 4).

$$\mathrm{CVF} = \text{left IJV} + \text{right IJV} + \text{left VV} + \text{right VV} \quad (3)$$

$$\Delta\mathrm{CVF} = \text{supine CVF} - \text{upright CVF} \quad (4)$$

Subjects who showed higher upright CVF compared to their supine postural CVF were termed as patients with an "abnormal" postural CVF control (absolute negative ΔCVF). A second analysis was performed based on the lowest quartile cut-off value of the ΔCVF for both the healthy controls (201.9 mL/min) and patients with MS (214.8 mL/min), with the participants split into two respective groups (lowest quartile ΔCVF group and the remaining quartiles group).

Statistical analysis

The statistical analysis was performed using SPSS 25.0 (IBM, Armonk, NY, USA). Clinical, demographic, and MRI-derived data were compared using χ^2-cross tabulation, Mann–Whitney U test, and Student's *t* test, as appropriate. Additionally, an analysis of covariance (ANCOVA) with correction for patients' age and sex was performed. To determine the normality of all variables, both Kolmogorov–Smirnov and Shapiro–Wilk tests were used. For the MRI-derived comparisons, group-specific Benjamini–Hochberg procedure for multiple comparison correction was applied. $p < 0.05$ after Benjamini–Hochberg correction was considered statistically significant using a two-tailed test.

Results

Demographic and clinical characteristics

The demographic and clinical characteristics of the 138 patients with MS and 49 healthy controls are summarized in Table 1. The MS group had a mean age of 53.6 ± 10.9 years, mean disease duration of 20.1 ± 10.6 years, a median Expanded Disability Status Scale score of 3.0 (interquartile range 1.9–6.0), and female ratio of 100/138 (72.5%). The patients were treated with disease-modifying therapies including interferon-β ($n = 46$, 33.3%), glatiramer acetate ($n = 39$, 28.3), natalizumab ($n = 5$, 3.6%), oral disease modifying medications ($n = 13$, 9.4%), other off-label treatments ($n = 6$, 4.4%) and 29 patients with MS (21%) were not treated. Additionally, the MS cohort consisted of 88 relapsing–remitting and 50 progressive MS patients. The heathy control group had a female ratio of 36/49 (73.5%) and was 51.4 ± 14.5 years old. There were no significant differences between the two groups regarding their sex ratio nor age.

The demographic and clinical characteristics between the relapsing–remitting and progressive subgroups are summarized in Supplement Table 1. Significant differences between highest and lowest ΔCVF quartiles of PMS patients were seen in sex (27 vs. 11 females; 69.2% vs. 100%; $p = 0.046$), disease duration (25.1 vs. 32.6 years, $p = 0.026$), as well as a median Expanded Disability Status Scale score (6.0 vs. 6.75, $p = 0.021$). There were no differences in terms of the type of disease-modifying therapy used between patients within the higher and lowest quartile (relapsing–remitting, $p = 0.781$ and progressive, $p = 0.716$).

Differences in bilateral internal jugular vein and vertebral vein flow between patients with MS and healthy controls

The venous flows within the bilateral jugular veins, vertebral veins, and total CVF measured in both postural positions of patients with MS and healthy controls are summarized in Table 2. There were no significant differences between patients with MS and healthy controls in their flow in supine and upright positions within the internal jugular veins

Table 1 Demographic and clinical characteristics of healthy controls and patients with multiple sclerosis

Demographic and clinical characteristics	HC group ($n=49$)	MS group ($n=138$)	p value HC vs. MS
Female, n (%)	36 (73.5)	100 (72.5)	0.892
Age in years, mean (SD)	51.4 (14.5)	53.6 (10.9)	0.334
Disease duration, mean (SD)	–	20.1 (10.6)	–
RRMS/PMS	–	88/50	–
EDSS, mean (IQR) median	–	3.6 (1.9–6.0) 3.0	–
Bladder/Bowel FS, mean (IQR) median	–	1.6 (0.0–3.0) 1.0	–
Absolute negative ΔCVF, n (%)	6 (12.2)	14 (10.1)	0.682
Lower quartile ΔCVF cut-off, mean ml/min	201.9	214.8	0.987
Disease-modifying therapies (DMT), n (%)			
Interferon-β	–	46 (33.3)	–
Glatiramer acetate	–	39 (28.3)	–
Natalizumab	–	5 (3.6)	–
Oral medications	–	13 (9.4)	–
Other off-label treatments	–	6 (4.4)	–
No disease-modifying therapy	–	29 (21.0)	–

Oral medications included dimethyl fumarate (5), fingolimod (5) and teriflunomide (3). Similarly, off-label treatments included intravenous immunoglobulins (4), methotrexate (1), and mitoxantrone (1)

χ^2-cross tabulation, and Student's t test were used accordingly. p-value lower than 0.05 was considered as significant

MS Multiple sclerosis, *SD* Standard deviation, *RRMS* Relapsing–remitting multiple sclerosis, *PMS* Progressive multiple sclerosis, *EDSS* Expanded Disability Status Scale, *FS* Functional score, *IQR* Interquartile range

Table 2 Flow measurements for bilateral internal jugular veins, vertebral veins and total cerebral venous flow in healthy controls and patients with multiple sclerosis

	HC ($n=49$)		MS ($n=138$)		Supine p-value	Upright p-value
	Supine	Upright	Supine	Upright		
Right IJV	541.6 (317.4)	152.8 (190.6)	497.6 (352.9)	159.5 (193.4)	0.442	0.836
Left IJV	295.1 (218.0)	92.4 (156.5)	372.7 (317.6)	139.9 (247.1)	0.062	0.209
Total IJV	836.8 (362.9)	245.3 (257.9)	870.3 (437.6)	299.5 (298.5)	0.632	0.260
Right VV	14.3 (14.6)	51.9 (56.5)	17.1 (24.2)	40.4 (46.9)	0.452	0.164
Left VV	7.5 (8.1)	39.9 (46.9)	10.8 (13.5)	37.9 (7.1)	0.114	0.788
Total VV	21.8 (18.8)	91.9 (86.9)	27.8 (31.9)	78.4 (73.1)	0.213	0.293
CVF	858.6 (362.3)	337.2 (254.4)	898.1 (429.1)	377.9 (294.7)	0.565	0.391

Data are reported as mean (standard deviation). All flow measurements are expressed in mL/min

Student's t test was used to compare the flow between MS and HCs. p-value lower than 0.05 was considered as significant. *MS* Multiple sclerosis, *HC* Healthy control, *IJV* Internal jugular vein, *VV* Vertebral vein, *CVF* Cerebral venous flow

($p=0.632$, $p=0.260$), vertebral veins ($p=0.213$, $p=0.293$) nor in total CVF ($p=0.565$, $p=0.391$), respectively.

Differences in MRI-derived outcomes in subjects with "abnormal" postural CVF control

Based on absolute negative postural control of venous flow, the patients with MS were classified as positive (normal) and negative (abnormal) postural venous groups. The differences in demographic, clinical, and MRI-derived outcome measures between the positive ($n=124$, 89.9%) and negative ($n=14$, 10.1%) postural venous control in patients with MS are shown in Table 3.

The MS group with abnormal postural CVF control had a significantly higher median Expanded Disability Status Scale score (3.5 vs. 3.0, $p=0.013$), and lower gray matter ($p=0.039$) and cortical ($p=0.044$) volumes, compared to normal postural control group (Table 3). The absolute negative ΔCVF group showed worse bladder and bowel function when compared to the absolute positive ΔCVF (mean 2.3 vs. 1.5, $p=0.052$), but this was not significant. Similarly to the MS group, there were 6 healthy controls (12.2%) that

Table 3 Differences in MRI and clinical outcomes measures between subjects with abnormal (negative) and normal (positive) ΔCVF in patients with multiple sclerosis

MRI and clinical outcome measures	HC group ($n=49$)	Positive ΔCVF ($n=43$)	Negative ΔCVF ($n=6$)	BH-corrected p value	MS group ($n=138$)	Positive ΔCVF ($n=124$)	Negative ΔCVF ($n=14$)	BH-corrected p value
Female, n (%)	36 (73.5)	32 (74.4)	4 (66.7)	0.687	100 (72.5)	88 (71.0)	12 (85.7)	0.242
Age in years, mean (SD)	51.4 (14.5)	51.6 (14.7)	49.6 (14.3)	0.755	53.6 (10.9)	53.2 (10.9)	56.9 (10.7)	0.229
Disease duration, mean (SD)	–	–	–	–	20.1 (10.6)	19.5 (10.2)	25.1 (12.9)	0.059
RRMS/PMS	–	–	–	–	88/50	81/43	7/7	0.258
EDSS, mean (IQR) median	–	–	–	–	3.6 (1.9–6.0) 3.0	3.4 (1.5–5.0) 3.0	4.9 (2.5–6.75) 6.5	**0.013**
Bladder/Bowel FS, mean (IQR) median	–	–	–	–	1.0 (0.0–3.0) 1.0	1.5 (0.0–3.0) 1.0	2.3 (1.0–3.0) 1.0	0.052
T1-LV	–	–	–	–	2.5 (6.0)	2.6 (6.1)	3.6 (5.3)	0.746
T2-LV	0.6 (1.4)	0.6 (1.5)	0.7 (1.4)	1.000	15.0 (18.5)	13.9 (17.8)	24.2 (23.2)	0.137
GMV	771.6 (63.4)	772.9 (64.6)	762.1 (58.4)	1.000	733.2 (61.2)	738.1 (59.8)	689.7 (57.3)	**0.039**
WMV	752.5 (46.2)	753.5 (44.9)	744.7 (58.7)	1.000	713.6 (44.3)	714.4 (45.6)	706.7 (31.6)	0.800
WBV	1524.0 (99.9)	1526.4 (99.5)	1506.8 (110.6)	1.000	1446.8 (92.5)	1452.5 (93.1)	1394.4 (71.9)	0.95
CV	627.4 (54.7)	627.9 (55.9)	623.7 (48.8)	0.992	595.4 (48.8)	599.4 (47.7)	559.9 (45.6)	**0.044**
LVV	36.4 (16.4)	36.3 (16.4)	37.4 (17.3)	1.000	532.3 (26.3)	52.1 (25.9)	62.9 (28.9)	0.287
DGM	60.0 (4.8)	60.1 (16.5)	59.9 (6.1)	1.000	54.1 (7.0)	54.6 (6.9)	50.0 (6.9)	0.065
Thalamus	20.1 (1.9)	20.2 (1.9)	19.7 (1.8)	1.000	17.9 (2.5)	18.1 (2.4)	16.4 (2.4)	0.060

χ^2-cross tabulation, Student's t test and analysis of covariance (ANCOVA) corrected for age and sex were used. p-value lower than 0.05 after Benjamini–Hochberg correction was considered as significant and shown in bold. Unless otherwise stated, data are reported as mean (standard deviation). Volumes are reported in milliliters

HC Healthy control, *MS* Multiple sclerosis, *EDSS* Expanded Disability Status Scale, *FS* Functional score, *GMV* Gray matter volume, *WMV* White matter volume, *WBV* Whole brain volume, *CV* Cortical volume, *LVV* Lateral ventricular volume, *DGM* Deep gray matter

presented with negative ΔCVF status. Although the small sample size limited the analysis, there was no significant difference between negative and positive ΔCVF healthy controls for demographic or any MRI-derived brain volume measures (Table 3).

Differences between subjects with the lowest and higher quartiles ΔCVF

The higher quartiles ΔCVF group of patients with MS were 68.3% (71/104) female, had a mean age of 53.4 ± 10.9 years old, a disease duration of 19.6 ± 10.9 years, and a median Expanded Disability Status Scale score of 3.0 (interquartile range 1.5–5.25). Among the patients within the higher ΔCVF quartiles group, the ratio of relapsing–remitting to progressive MS patients was 65/39. On the other hand, the lowest ΔCVF quartile had a female ratio of 29/34 (85.3%), was on average 54.2 ± 11.4 years old, had a disease duration of 21.7 ± 12.0 years, and had a median Expanded Disability Status Scale score of 3.0 (interquartile range 2.0–6.5). Similarly, the relapsing–remitting to progressive MS distribution of the lowest ΔCVF quartile was 23/11, respectively. Within the quartile comparison, there were no significant differences observed for sex, age, disease duration, disease course or disability level. All demographic and clinical characteristics of the quartile-based MS groups are shown in Table 3.

Comparably, the higher quartiles of the healthy control group had a ratio of females of 28/37 (75.7%) and was on average 53.8 ± 13.7 years old, whereas the lowest quartile had the average age of 43.9 ± 14.9 years old and had female ratio of 8/12 (66.7%). Participants in the lowest quartile group were generally younger than those in the higher quartile group ($p=0.038$).

MRI-derived outcome measures between lower and higher quartiles' ΔCVF for both the patients with MS patients and healthy controls are presented in Table 4. The lowest ΔCVF quartile MS group had significantly higher T1-lesion volume ($p=0.033$), T2-lesion volume ($p=0.032$) and lower deep gray matter ($p=0.043$) and thalamus

Table 4 Differences in MRI and clinical outcomes measures between the lowest quartile and higher quartiles in healthy controls and patients with multiple sclerosis

MRI and clinical outcome measures	HC group ($n=49$)	Higher quartiles ($n=37$)	Lowest quartile ($n=12$)	p value	MS group ($n=138$)	Higher quartiles ($n=104$)	Lowest quartile ($n=34$)	BH-corrected p value
Female, n (%)	36 (73.5)	28 (75.7)	8 (66.7)	0.377	100 (72.5)	71 (68.3)	29 (85.3)	0.054
Age in years, mean (SD)	51.4 (14.5)	53.8 (13.7)	43.9 (14.9)	**0.038**	53.6 (10.9)	53.4 (10.9)	54.2 (11.4)	0.727
Disease duration, mean (SD)	–	–	–	–	20.1 (10.6)	19.6 (10.9)	21.7 (12.0)	0.318
RRMS/PMS	–	–	–	–	88/50	65/39	23/11	0.605
EDSS, mean (IQR) median	–	–	–	–	3.6 (1.9–6.0) 3.0	3.5 (1.5–5.25) 3.0	3.9 (2.0–6.5) 3.0	0.294
Bladder/Bowel FS, mean (IQR) median	–	–	–	–	1.6 (0.0–3.0) 1.0	1.4 (0.0–3.0) 1.0	1.9 (0.0–3.0) 1.0	0.336
T1-LV	–	–	–	–	2.5 (6.0)	1.8 (3.8)	5.2 (9.9)	**0.033**
T2-LV	0.6 (1.4)	0.7 (1.5)	0.4 (0.9)	1.000	15.0 (18.5)	12.0 (13.9)	24.1 (26.6)	**0.32**
GMV	771.6 (63.4)	768.9 (59.2)	779.6 (77.2)	1.000	733.2 (61.2)	738.7 (60.6)	716.4 (60.6)	0.058
WMV	752.5 (46.2)	750.5 (45.1)	758.3 (51.2)	0.993	713.6 (44.3)	714.2 (45.4)	711.7 (41.5)	0.860
WBV	1524.0 (99.9)	1519.5 (92.7)	1537.9 (122.9)	1.000	1446.8 (92.5)	1452.8 (93.8)	1428.1 (87.2)	0.188
CV	627.4 (54.7)	624.6 (51.3)	635.9 (65.7)	1.000	595.4 (48.8)	599.8 (48.3)	581.9 (48.4)	0.068
LVV	36.4 (16.3)	37.9 (17.2)	31.8 (13.3)	1.000	532.3 (26.3)	50.5 (24.7)	61.5 (29.6)	0.054
DGM	60.0 (4.8)	59.9 (4.6)	60.5 (5.6)	1.000	54.1 (7.0)	54.9 (6.8)	51.7 (7.2)	**0.043**
Thalamus	20.1 (1.9)	20.0 (1.9)	20.3 (1.9)	1.000	17.9 (2.5)	18.2 (2.4)	17.0 (2.5)	**0.033**

χ^2-cross tabulation, Student's t test and analysis of covariance (ANCOVA) corrected for age and sex were used. p-value lower than 0.05 after Benjamini–Hochberg correction was considered as significant and shown in bold. The low quartile cut-off value of the ΔCVF for the groups were 201.9 mL/min and 214.8 mL/min (HC and MS, respectively). Unless otherwise stated, data are reported as mean (standard deviation). Volumes are reported in milliliters

HC Healthy control, *MS* Multiple sclerosis, *EDSS* Expanded Disability Status Scale, *FS* Functional score, *GMV* Gray matter volume, *WMV* White matter volume, *WBV* Whole brain volume, *CV* Cortical volume, *LVV* Lateral ventricular volume, *DGM* Deep gray matter

($p=0.033$) volumes. Although the small sample size limited the analysis, there were no significant differences in any MRI-derived outcome measures between the lowest and higher quartiles ΔCVF healthy control groups.

A separate analysis within the relapsing–remitting and progressive MS subgroups was performed. The differences in MRI-derived outflow measures within both subgroups are shown in Supplement Table 2. We found no significant differences between higher and lowest quartiles ΔCVF RRMS subgroups with respect to the volumetric outcomes. The lowest quartiles ΔCVF progressive MS subgroup had significantly lower thalamus volume ($p=0.049$) when compared to the higher quartiles ΔCVF group.

Discussion

In the present study, there was no difference in the postural control of the venous flow between patients with MS and healthy controls. The inflammatory and neurodegenerative MS pathology was more severe in patients with autonomic impairment, as measured by orthostatic venous dysfunction. Although this impairment was manifested in a similar ratio of healthy controls, patients with MS and abnormal venous postural control (in terms of both absolute and quartile analysis) had longer disease duration, higher clinical disability scores, higher lesion burden, and more gray matter atrophy. The worse bladder and bowel functional scores within patients with abnormal venous postural control provide some concurrent validity of the measure used. Although the small sample size limited meaningful analysis, the healthy controls did not differ in either demographic or MRI-derived volumetric measures.

Cerebral venous drainage in supine body posture is mainly attributed to the internal jugular veins, however when positioned upright, the venous drainage shifts and directs through the vertebral venous system [13, 15, 28]. This gravity-driven increase in jugular resistance and the collapse of the internal jugular veins allow control of the cerebral venous pressure despite the changes of the physical and perfusion forces [14]. The cerebral venous blood flow (referred to as CVF) measured in either supine or upright positions

reflects the current and transient state of the venous vascular system, whereas the change of the venous flow prompted by the change in body posture (referred as ΔCVF) provides dynamic information of blood flow control. As proper autonomic nervous system functioning might have an active role in the aforementioned control of orthostatic venous flow, potential MS-associated autonomic system impairment may lead to inadequate outflow change patterns. Similarly to the principles of the orthostatic hypotension diagnosis, inadequate venous blood flow response would yield additional information on the autonomic pathology. These findings are increasingly of interest since it has been shown that not only has autonomic dysfunction been associated with certain MS symptomatology, but it also can correlate with future progression of clinical disability [29].

In addition to the well-described peripheral and brainstem organization of the autonomic nervous system, recent task-based fMRI studies and neurological lesion-damage studies have localized the cortical autonomic network to the frontoinsular, anterior cingulate cortices, and midcingulate cortices [30]. The left and right hemispheric networks located in the frontoinsular and cingulate cortex have been shown to be crucial in maintaining basal parasympathetic and responsive sympathetic outflow, respectively [19]. Therefore, more advanced gray matter, cortical, and deep gray matter atrophy observed in patients with MS with an inadequate postural response are in line with the localization of autonomic nervous system structures within wide cortical networks [19]. Salient damage to the cortex by cortical MS lesions may result in impairment of the maintenance of autonomic homeostasis as previously shown in stroke patients [31]. Additionally, cortical thinning, a hallmark of the MS neurodegenerative process, may disrupt the autonomic nervous system circuits and contribute to abnormal vascular coupling and perfusion control. In similar fashion, a recent review emphasized the effect of the autonomic nervous system and its influence on brain volume [32]. The authors suggested that constant dynamic changes of brain volume can be a result of cerebral blood volume regulation governed by the autonomic nervous system [32]. Concurrently, impairment of cerebrovascular reactivity and regulation of the cerebral blood flow have been seen in patients with MS and in the classical settings of autonomic dysfunction in familial amyloidotic polyneuropathy [33, 34].

A previous study demonstrated that patients with MS and healthy controls initially had an equal supine internal jugular vein flow; however, while switching into the upright position, patients with MS did not redirect the venous flow to the vertebral plexus and had sustained higher internal jugular vein flow indicative of a supine posture [35]. The authors hypothesized that this finding might reflect an ANS autonomic dysfunction and orthostatic dysregulation [35]. Similarly, recent findings also showed that negative ΔCVF status can differentiate patients with MS versus healthy controls [9]. The same research group also proposed a ΔCVF cutoff value of $\leq$ 503.24 mL/min as a sensitive and specific differentiation between patients with MS and patients with other neurological diseases [12]. However, in this study, the absolute delta CVF was calculated by measuring cross-sectional areas in different tracts of the internal jugular veins and vertebral veins (distal vs. proximal tracts), and the different quantity of CVF was considered. Furthermore, similar findings reported that negative ΔCVF was present in 52.9% of relapsing–remitting and 75.9% of progressive MS, versus only 13.4% of healthy controls [10]. Contrary to those findings, we did not detect differences in the prevalence of abnormal ΔCVF between the patients with MS and healthy controls. The lowest quartile cut-off value of the ΔCVF was not significantly different (201.9 mL/min and 214.8 mL/min for healthy controls and patients with MS, respectively). In comparison to the aforementioned studies, we used an older cohort of patients with MS and healthy controls. The significant age-dependent decline of both sympathetic and parasympathetic responses have been previously characterized and may have influenced our findings [36].

Based on previous arterial studies, the Valsalva maneuver (a profound but transient change in cerebral and systemic blood flow) can cause changes in the blood pressure that are subdivided into four main phases. The fourth phase of the maneuver has a characteristic arterial flow overshoot mechanism which exceeds the baseline value [37]. The process of overshoot contributes to an active autonomic regulation and can be successfully inhibited by pharmacological interventions [38]. Furthermore, a Doppler sonography study using the Valsalva maneuver showed a similar phase IV venous overshoot mechanism which was larger when compared to the arterial one by a factor of $>$ 100% [39]. Additionally, due to the lack of temporal delay when compared to the arterial contra-part, the venous overshoot can possibly implicate an active involvement of venoconstriction [39]. As mentioned previously, these findings of active venoconstriction coincide with the discovery of smooth muscle cells within the wall of the sinus bridging veins, which are generally considered absent in the wall of the cerebral venous system [39, 40]. All these findings point to an active venous outflow control regulated by the autonomic nervous system.

After averaging the Doppler flow measures, we did not detect any differences either in blood volume or in postural flow patterns between healthy controls and patients with MS. Our flow data confirm the previously described discrepancies in the bilateral venous flow, potentiating the right-sided dominance manifested in both groups [41–43]. The twofold disparity of venous flow detected in the supine versus upright position suggests an alternative upright venous drainage pathway. The partial increase of venous flow in the vertebral veins while positioned upright

does not provide sufficient explanation of the decreased internal jugular vein venous outflow seen in both healthy controls and patients with MS. A recent description of the structural and functional features of central nervous system lymphatic vessels may provide the missing link in the puzzle of venous, interstitial, and cerebrospinal fluid drainage [44].

This study is not without limitations. Due to the unavailability of arterial flow measures acquired from different postural positions, we utilized the orthostatic venous flow data in order to derive a measure of orthostatic vascular control. Although the venous postural flow patterns have some concurrent validity to their arterial counterpart, a direct use of arterial postural measures is critically warranted. Furthermore, the limitations of venous Doppler blood flow assessments are substantially greater than arterial flow measures and are elsewhere comprehensively discussed [45]. Fingolimod, a disease-modifying therapy for MS, can cause changes of the heart rate (bradycardia) and atrioventricular block; however these symptoms usually subside during the first month of treatment or when the treatment is discontinued, and only a few patients in the present study were treated with this drug [46]. Finally, the study utilized an exclusion criterion for patients with MS that received corticosteroid infusions 30 days before the study entry, since it can additionally cause perturbations within the catecholamine levels that would result in changes of autonomic functioning [29].

The study does not provide information of whether the presence of abnormal postural venous outflow may be a result of MS-derived neurodegeneration, overall aging effect, or if it precedes brain atrophy. Due to the similar healthy control prevalence and the aging profile of the population used, the current results suggest that this finding is not an MS-specific phenomenon. However, prospective age- and sex-matched studies with baseline flow characteristics and use of validated autonomic nervous system tests/questionnaires may clarify these findings.

Conclusion

There were no differences in the postural venous outflow between patients with MS and healthy controls. This study did not corroborate the previously reported high level of abnormal postural venous control in patients with MS. However, we found that if present, the abnormal postural venous flow may be associated with higher inflammatory and neurodegenerative pathology in patients with MS. The potential link between postural venous blood flow control with the MS pathophysiology and autonomic nervous system impairment, if any, remains largely unknown.

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