Internal jugular vein narrowing and body mass index in healthy individuals and multiple sclerosis patients

Christopher Magnano,[1,2] Pavel Belov,[1] Jacqueline Krawiecki,[1] Jesper Hagemeier,[1] Robert Zivadinov[1,2]

[1]Department of Neurology, Buffalo Neuroimaging Analysis Center, School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY; [2]MRI Clinical and Translational Research Center, School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, USA

Abstract

Internal jugular vein (IJV) narrowing has been implicated in central nervous system (CNS) disorders. Body mass index (BMI) is a cardiovascular risk factor that has been also linked to CNS diseases, however it is unknown whether a relationship exists between IJV narrowing and BMI. The objectives were to assess the relationship between IJV cross-sectional areas (CSA) and BMI in healthy individuals (HI) and multiple sclerosis (MS) patients. A total of 388 subjects (194 age- and sex-matched HI and MS patients) received magnetic resonance venography and structural brain magnetic resonance imaging at 3T. Region of interest analysis was performed using a semiautomated contouring-thresholding technique to determine the minimum CSA of the IJVs at C2/C3, C5/C6, and C7/T1 cervical levels. Partial correlation analyses were used to determine the associations. Increased BMI was related to increased IJV CSA at lower cervical levels ($r=0.240$, $P<0.0001$ at C5/C6 and $r=0.293$, $P<0.0001$ at C7/T1) in both MS patients and HI. Both MS and HI, showed associations between increased BMI and IJV CSA measures, particularly at lower cervical locations, in individual group analyses. No differences in association between BMI and IJV CSA were observed between HI and MS patients. Relationship between IJV CSA and BMI were not significant at upper cervical locations in the studied groups. Increased BMI is associated with IJV CSA widening, rather than narrowing, at lower cervical levels in both MS patients and HI. This finding warrants further investigation, but indicates that BMI can obscure interpretation of IJV CSA narrowing.

Introduction

Blood is supplied to the brain and spinal cord by two sets of branches from the dorsal aorta.[1] The vertebral arteries arise from the subclavian arteries, while the internal carotid arteries branch from the common carotid arteries.[1] Deoxygenated blood is drained from the brain and spinal cord by the venous system, particularly the internal jugular veins (IJVs), which connect the sinuses to the vena cava.[2,3] The cerebral venous system is considered most important contributor for maintenance of adequate brain perfusion, in order to meet the metabolic needs necessary for normal cerebral function.[2] Venous drainage from the cerebral hemispheres consists of two systems: the superficial, which drains blood from the cortex and superficial white matter by cortical veins, and is collected by the dural sinuses;[4] and the deep venous system, which contains approximately 70% of the total blood volume, and incorporates small veins and venules for the majority of its composition.[4] In contrast to the symmetric arterial system, the venous system is asymmetric and highly heterogeneous.[4] IJV morphology has previously been investigated with respect to aging and gender differences in healthy individuals (HI),[5,6] in addition to a number of central nervous system (CNS) diseases, including multiple sclerosis (MS), Alzheimer's disease and Parkinson's disease.[4] Numerous recent studies have focused on morphological and hemodynamic venous jugular flow abnormalities in MS patients and HIs.[4,7-11] However, it is unknown at this time whether the IJV narrowing has any pathological significance, or is just a normal physiologic variant.

Body mass index (BMI) is a standard measure of degree of obesity. It is also a cardiovascular risk factor that has been linked to CNS diseases.[12-15] We hypothesized that, as a result of obesity, we would find a reduced IJV cross-sectional area (CSA) due to venous constriction in subjects with large BMIs. Venous narrowing can be caused either directly due to intraluminal defects or hypoplasia, or as a result of blockages such as venous thrombosis.[13,16] As BMI is linked with increased risk of CNS diseases, we expected to find more pronounced narrowing in a cohort of MS patients when compared with HIs. We were also interested to explore the cervical level at which CSA reduction would impact these associations. Therefore, we examined the relationship between the IJV CSA at three different cervical levels in healthy and diseased subjects with a spectrum of body mass indices.

Correspondence: Robert Zivadinov, Department of Neurology, School of Medicine and Biomedical Sciences, Buffalo Neuroimaging Analysis Center, 100 High St., Buffalo, NY 14203, USA.
Tel. 716.859.3579 - Fax: 716.859.4005.
E-mail: rzivadinov@bnac.net

Key words: healthy individuals, multiple sclerosis, internal jugular veins, cross-sectional area, body mass index, magnetic resonance imaging, magnetic resonance venography.

Conflict of interests: the authors declare no potential conflict of interests.

Funding: RZ received funding for consultancy from Teva Pharmaceuticals, Biogen Idec., EMD Serono, Novartis, Sanofi-Genzyme.

Received for publication: 29 July 2014.
Revision received: 28 October 2014.
Accepted for publication: 20 November 2014.

Veins and Lymphatics 2014; 3:4632
doi:10.4081/vl.2014.4632

Materials and Methods

Subjects

This prospective, single-center, cross-sectional study included 388 subjects, with 194 consecutive HIs with no evidence of neurological disease and 194 consecutive relapsing remitting (RR) MS patients being enrolled (matching 1:1). Inclusion criteria included completion of magnetic resonance imaging (MRI) screening to ensure no MRI-prohibitive medical history. Cardiovascular risk factors were collected from all participants in-person by a trained interviewer with cross-examination of medical records. All participants were assessed with a structured environmental questionnaire containing information about medical history (illnesses, surgeries, medications, etc.), as well as cardiovascular risks, including history of hypertension, smoking, or heart disease (which was defined to include congestive heart failure, heart attack, arrhythmia, valvular disease, heart murmurs, enlarged heart, heart surgeries, palpitations, or any other category that would necessitate medical therapy). Height and weight were assessed to determine BMI. Physical and neurological examination were obtained in all study particpants. All subjects were required to meet the health screen requirements on physical examination and history of known vascular abnormalities also precluded enrollment in

the study. HIs were recruited among hospital personnel and local advertisement respondents, while the MS patients were enrolled at the Center specialized for demyelinating diseases. All study experiments were performed in accordance with the relevant guidelines and regulations. The study was approved by the local Institutional Review Board, and informed consent was obtained from all subjects.

Image acquisition

All subjects were examined on a GE 3.0T Signa Excite HD 12.0 Twin Speed 8-channel scanner (General Electric, GE, Milwaukee, WI, USA) with a maximum slew rate of 150T/m/s and maximum gradient amplitude in each orthogonal plane.

A 2-dimensional magnetic resonance venography (MRV) sequence was acquired for all IJV CSA measurements. The MRV was acquired with 150, 1.5mm-thick slices using a 320×192 matrix (frequency x phase) with a 22.0 cm field of view (FOV) and a phase field of view (pFOV) of 75% for a resolution of .69×1.15×1.5 mm^3. Additional imaging parameters included echo time (TE)/repetition time (TR)/flip angle (FA) of 4.3 ms/14 ms/70°, and a bandwidth (BW) of 31.25 kHz, for a total acquisition time of 5:19 min. MRV was acquired in a *true* (non-obliqued) axial orientation with one average, and no parallel imaging techniques were employed.

A 2-dimensional fluid-attenuated inversion-recovery (FLAIR) sequence was acquired for assessment of T2 hyperintense lesion pathology. FLAIR scans were 3-mm thick slices with no gap, TE/TI/TR=120/2100/8500 ms, flip angle=90°; with a 256×256 matrix and a 25.6 cm FOV for an in-plane resolution of 1x1 mm^2 with a phase FOV of 75% and one average.

Image analyses

Cross-sectional area analyses

IJV assessment was performed using CSA region of interest (ROI) analysis on the 2D MRV with the Java Image Manipulation Tool (JIM) version 5.0 (http://www.xinapse.com) at specific cervical locations blinded to the subjects' status. Briefly, the sequence was viewed orthogonally to assess which slices corresponded to the desired anatomical coverage, namely C2-C3, C4, C5-C6, and C7-T1. Within each of these locations, the operator determined the slice on which the IJV came to a minimum, and then used the ROI Toolkit to select the right and left IJVs. Most commonly, this was accomplished using the Contour ROI tool, using the automated Preview Contours tool to best select its edges. When necessary, the operator manually adjusted the ROI boundary. Reproducibility was assessed using two operators performing CSA analysis on a set of 25 MRVs twice, with analyses a minimum of 2 weeks apart. Operators were blinded to each other's ROI assessments, as well as to their own prior set of ROIs. Intra- and inter-operator reproducibility was assessed using the intra-class correlation (ICC), with corresponding P- and q-values.

T2 hyperintense lesion determination

T2-weighted hyperintense lesion number and volume were assessed using a semiautomated edge detection contouring/thresholding technique on FLAIR images.[17]

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (IBM Inc, version 21.0). The demographic and clinical differences between genders were tested using Student's *t*-test and chi-square tests. BMI and CSA measures were compared using partial correlation analyses. Group comparisons were calculated using Student's *t*-test. Due to multiple comparisons, only a nominal P-value<0.01, was considered statistically significant using two-tailed tests.

Table 1. Demographic and clinical characteristics of healthy individuals and multiple sclerosis patients.

	Total (N=388)	HI (N=194)	MS (N=194)	P-value
Age°	42.6 (15.8) 44	43.0 (17.5) 46	42.2 (13.9) 43	0.629**
Sex (M/F)	126/262	63/131	63/131	1.00**
BMI	26.8 (5.7) 25.8	26.8 (5.7) 25.8	26.8 (5.8) 25.8	0.938**
Heart disease	51/264 (16.2%)	20/142 (12.3)	31/122 (20.3)	0.074**
Hypertension	57/263 (17.8%)	19/150 (11.2)	38/113 (25.2)	0.001*
Smoking	132/205 (39.2%)	58/122 (32.2)	74/83 (47.1)	0.006*
Number of subjects with T2° hyperintense lesions	246/121 (67)	65/119 (35.3)	181/2 (98.9)	<0.0001*
Number of T2° hyperintense lesions	15.4 (20.5) 7	2.8 (7.1) 0	28.1 (21.8) 22	<0.0001*
Volume of T2° hyperintense lesions (mL)	5.79 (11.5) 0.581	0.248 (1.13) 0	11.4 (14.2) 5.84	<0.0001*
Age° at onset	N/A	N/A	31.0 (12.8) 30.0	N/A
Disease duration in years	N/A	N/A	12.0 (9.4) 10.0	N/A
EDSS	N/A	N/A	2.5 (1.3) 2.0	N/A

HI, healthy individuals; MS, multiple sclerosis; BMI, body mass index; EDSS- expanded disability status scale. P-values were calculated using Student's *t*-test and chi-square tests: *P-values less than 0.01 considered significant; **P-values less than 0.05 were considered trends. °Age and T2 lesion characteristics are presented as mean (standard deviation) median. Categorical variables (cardiovascular risk factors) are #Yes/Total # (%).

Table 2. Internal jugular vein cross-sectional area values and standard deviations in healthy individuals and multiple sclerosis patients across multiple cervical locations.

	All subjects	HI	MS	P-value
C7/T1	115.9 (73.2)	118.0 (79.3)	113.8 (66.6)	0.575
C5/C6	95.3 (58.5)	97.4 (60.2)	93.2 (56.7)	0.473
C2/C3	66.1 (29.4)	66.7 (31.4)	65.5 (27.2)	0.691

HI, healthy individuals; MS, multiple sclerosis. The cross-sectional area is expressed in millimeter square. Values reported are mean (standard deviation). P-values were calculated using Student's t-test and chi-square tests.

Table 3. Association of internal jugular vein cross-sectional area and body mass index in healthy individuals and multiple sclerosis patients across multiple cervical locations.

	All subjects	HI	MS
Age vs BMI	0.169 (0.002)*	0.062 (0.416)**	0.262 (0.001)*
C7/T1	0.293 (0.000)*	0.294 (0.000)*	0.296 (0.000)*
C5/C6	0.240 (0.000)*	0.247 (0.001)*	0.234 (0.002)*
C2/C3	0.045 (0.411)**	0.078 (0.324)**	0.009 (0.909)**

HI, healthy individuals; MS, multiple sclerosis; BMI, body mass index. Values reported are partial correlations (P-value). *P-values less than 0.01 considered significant; **P-values less than 0.05 were considered trends.

Results

Demographic characteristics

Demographic characteristics are presented in Table 1. HI and MS subjects were age- and sex-matched. As expected, significant differences were found between HIs and MS subjects in terms of cardiovascular risk factors, smoking, and number and volume of T2 hyperintense lesions. BMI was not significantly different between the study groups. The MS patients were on disease-modifying treatment including interferon β 1a, glatiramer acetate and natalizumab.

Reproducibility of the cross-sectional area measurement

Inter- and intra-operator reproducibility was found to be highly significant with strong ICC values and corresponding P-values (ICC>0.69 for inter-operator with P<0.001, and ICC>0.84 for intra-operator, with P<0.001 at all levels and for all operators).

Internal jugular vein cross-sectional area morphology

IJV CSAs was greater at lower cervical levels, ranging from a mean of 66.1 mm^2 at C2/C3 to115.9 mm^2 at C7/T1. Breakdown at each level is shown in Table 2.

Cross-sectional area correlations with body-mass index

As shown in Table 3, greater IJV CSA was strongly correlated with increased BMI (r≥0.234, P≤0.002 for all) at lower cervical levels (C5/C6 and C7/T1), whereas this association was not detected at upper cervical levels (C2/C3 nor C4). The association was significant in all subjects, as well as individually in HI and MS patients groups. There were no differences between the study groups, as the associations were similar in terms of strength and significance, irrespective of disease status (Tables 2 and 3; Figure 1).

Age interaction with cross-sectional area association with body-mass index

As shown in Table 3, BMI was associated with age in all subjects (r=0.169, P=0.002) and in MS patients (r=0.262, P=0.001). BMI was not associated with age in HI (r=0.062, P=0.416). However, the BMI and IJV CSA association was found to be age independent in partial correlation analysis, across all groups (*data not shown*).

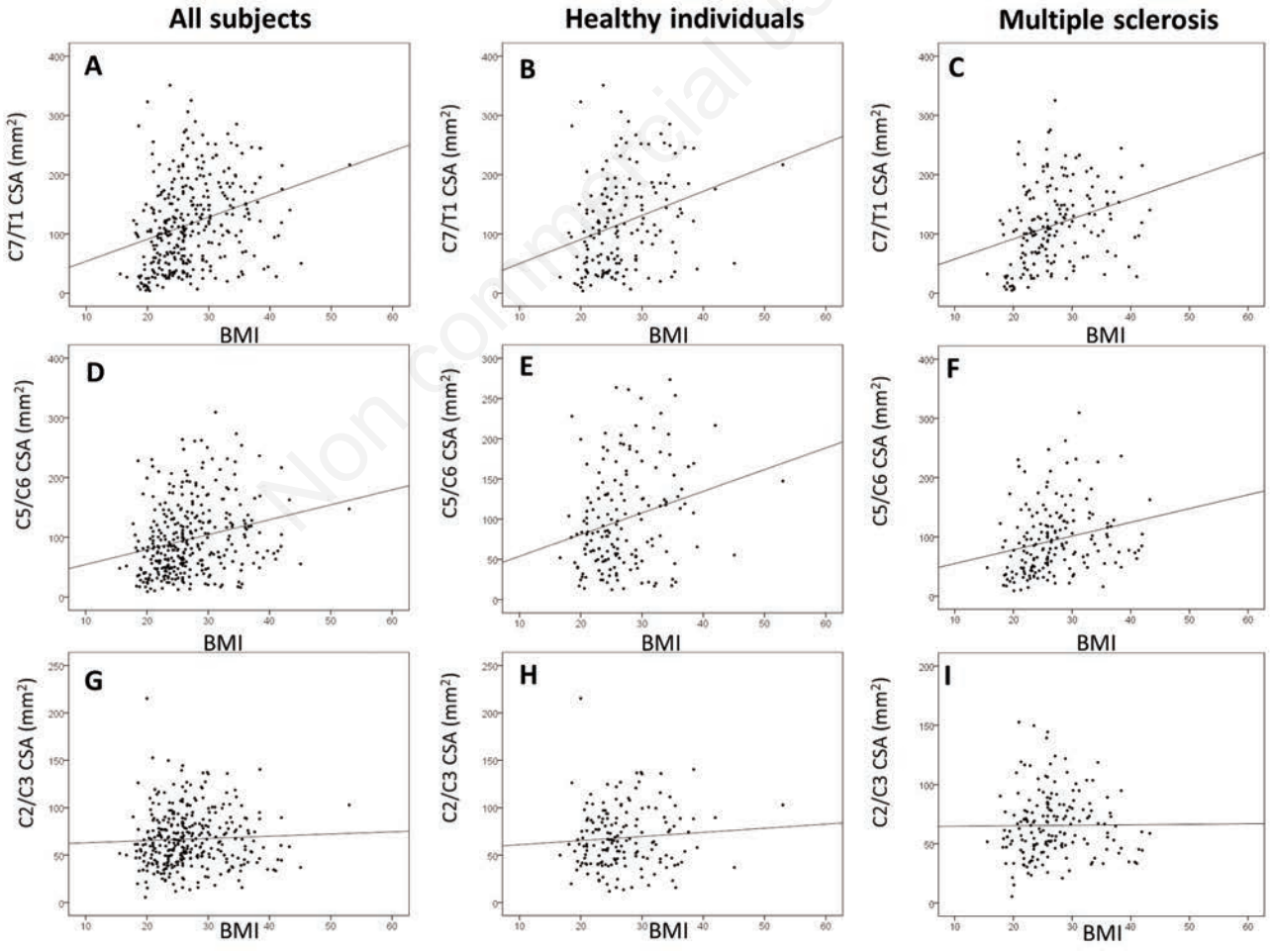

Figure 1. Associations between body mass index (BMI) and cross-sectional area at levels C7/T1 (A, B, C), C5/C6 (D, E, F), and C2/C3 (G, H, I).

Discussion

We investigated the association of IJV CSA on MRV with BMI in MS patients and HIs, and found a relationship between the two at the lower cervical levels, independent of any age effects. Findings were similar in both HIs and MS patients, suggesting that this relationship is independent of the disease state.

While our initial hypothesis was that IJV narrowing would be associated with increased BMI, actually the results showed the opposite; namely, that as the BMI increased, so did the IJV CSA. These findings suggest that the more obese a subject is, rather than narrowing, their IJV CSA is actually enlarging. This could be due to the fact that, assuming a constant volume of blood to pump, that more obese subjects will thus have lower flow rates, although our study was limited to only structural and did not include functional outcomes. As subjects with larger BMIs tend to be more sedentary and less mobile, their oxygen demand will decrease, and thus both their oxygen supply via arterial blood, as well as deoxygenated clearance via the venous system, will decrease, leading to reduced flow rates.

While our hypothesis was that the location of vascular assessment would play a role in IJV CSA, this was only true to a point: C5/C6 and C7/T1 had a similar relationship with BMI, whereas C2/C3 did not. We suspect that this may be due to the fact that there is a high degree of heterogeneity at upper cervical levels (C2-C3), as evidenced by the increased prevalence of collaterals. Since the correlations between IJV CSA and BMI seem to be indicative of total flow at lower levels (where the vast majority of venous flow is drained through the IJVs), it is possible that the exclusion of additional venous collateral assessment could be confounding our results at upper cervical levels. Therefore further exploration is warranted regarding this issue.

Age and BMI were associated across the entire cohort and in the MS patients, but not in the HIs. However, we speculate that the fact that BMI and CSA relationship was age independent in HI, suggests that the age dependence of BMI in MS patients may be due to decreased level of activity, rather than strictly age, and would warrant further study.

While we also investigated differences in association between IJV CSA and BMI between MS patients and HI, none was observed, consistent with other groups' findings.[18-20] This suggests that CSA and BMI measures are unrelated to the disease status. Any differences are most likely functional (*i.e.* flow-related) rather than structural (*i.e.* due to morphology). This study was limited in scope to structural assessment of the IJVs; flow quantification can provide additional information, as other groups are currently investigating.

Additionally, our study had several other limitations. The focus on the IJV CSA neglected any collateral flow; future work should examine collateral vein measures, particularly at upper cervical locations. It would be also interesting to examine the level of activity, in order to explore how this affects the relationship between IJV CSA and BMI in MS and HIs. This work only examined the minimum CSA at each cervical location, and an automated analysis of the CSA at each slice would offer a more volumetric approach. Moreover, only RR MS patients were enrolled in the study, in order to allow age-matching with HI. It could be that secondary-progressive MS patients show different relationship between IJV CSA and BMI. Even within only examining structural involvement, the MRV technique we used is beneficial for detecting venous compression, but intra-luminal restrictions may be concealed; use of Doppler technique may be useful in this direction.

Conclusions

Increased BMI is associated with IJV CSA widening, rather than narrowing, at lower cervical levels in both MS patients and HI. This finding warrants further investigation, but indicates that BMI can obscure interpretation of IJV CSA narrowing.

References

1. Purves D, Williams SM. Neuroscience, 2nd ed. Sunderland, MA: Sinauer Associates; 2001.
2. Schaller B. Physiology of cerebral venous blood flow: from experimental data in animals to normal function in humans. Brain Res Brain Res Rev 2004;46:243-60.
3. Ciuti G, Righi D, Forzoni L, et al. Differences between internal jugular vein and vertebral vein flow examined in real time with the use of multigate ultrasound color Doppler. AJNR Am J Neuroradiol 2013;34:2000-4.
4. Zivadinov R, Chung CP. Potential involvement of the extracranial venous system in central nervous system disorders and aging. BMC Med 2013;11:260.
5. Gur RC, Mozley PD, Resnick SM, et al. Gender differences in age effect on brain atrophy measured by magnetic resonance imaging. Proc Natl Acad Sci USA 1991;88:2845-9.
6. Resnick SM, Pham DL, Kraut MA, et al. Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. J Neurosci 2003;23:3295-301.
7. Zivadinov R, Marr K, Cutter G, et al. Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS. Neurology 2011;77:138-44.
8. Zamboni P, Galeotti R. The chronic cerebrospinal venous insufficiency syndrome. Phlebology 2010;25:269-79.
9. Zamboni P, Galeotti R, Menegatti E, et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 2009;80:392-9.
10. Zamboni P, Menegatti E, Occhionorelli S, Salvi F. The controversy on chronic cerebrospinal venous insufficiency. Veins and Lymphatics 2013;2:e14.
11. Sisini F, Gianesini S, Menegatti E, et al. On the consistency of flow rate color Doppler assessment for the internal jugular vein. Veins and Lymphatics 2014;3:1863.
12. Kim AY, Rhim H, Park M, et al. Venous thrombosis after radiofrequency ablation for hepatocellular carcinoma. AJR Am J Roentgenol 2011;197:1474-80.
13. Stam J. Thrombosis of the cerebral veins and sinuses. N Engl J Med 2005;352:1791-8.
14. Stambo GW, Grauer L. Transhepatic portal venous power-pulse spray rheolytic thrombectomy for acute portal vein thrombosis after CT-guided pancreas biopsy. AJR Am J Roentgenol 2005;184:S118-9.
15. Kim SA, Lim SY. A case of stent thrombosis occurred at 5 years after sirolimus-eluting stent implantation. Chonnam Med J 2011;47:124-6.
16. Lim BG, Kim YM, Kim H, et al. Internal jugular vein thrombosis associated with venous hypoplasia and protein S deficiency revealed by ultrasonography. J Anesth 2011;25:930-4.
17. Zivadinov R, Heininen-Brown M, Schirda CV, et al. Abnormal subcortical deep-gray matter susceptibility-weighted imaging filtered phase measurements in patients with multiple sclerosis: a case-control study. Neuroimage 2012;59:331-9.
18. Zaniewski M, Kostecki J, Kuczmik W, et al. Neck duplex Doppler ultrasound evaluation for assessing chronic cerebrospinal venous insufficiency in multiple sclerosis patients. Phlebology 2013;28:24-31.
19. Farina M, Novelli E, Pagani R. Cross-sectional area variations of internal jugular veins during supine head rotation in multiple sclerosis patients with chronic cerebrospinal venous insufficiency: a prospective diagnostic controlled study with duplex ultrasound investigation. BMC Neurol 2013;13:162.
20. Krsmanovic Z, Zivkovic M, Lepic T, et al. Small internal jugular veins with restricted outflow are associated with severe multiple sclerosis: a sonographer-blinded, case-control ultrasound study. BMC Neurol 2013;13:90.