Doppler Ultrasound Examination of Multiple Sclerosis Patients and Control Participants: Inter-observer Agreement and Association with Disease

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WHAT THIS PAPER ADDS

Chronic cerebrospinal venous insufficiency (CCSVI) hypothesis has generated extensive debate around the world. CCSVI has been proposed as a major risk factor for multiple sclerosis (MS). Many studies have been devoted to confirming the CCSVI hypothesis, with contradictory results. The first diagnostic tool to detect CCSVI is ultrasound, but the reliability of the examination is unclear. So the aim of the current study was to assess inter-observer agreement between two independent examiners as regards the sonographic criteria of CCSVI and to compare the ultrasound findings in Finnish MS patients at different stages of the disease with age- and sex-matched healthy control participants.

Objective: Chronic cerebrospinal venous insufficiency (CCSVI) has been proposed as a major risk factor for multiple sclerosis (MS). The aim of this study was to assess inter-observer agreement between two ultrasound examiners and to compare findings in MS patients and control participants.

Methods: A prospective, blinded, controlled study of MS patients diagnosed within 2 years (MS $\leq$ 2, $n = 39$), patients diagnosed more than 10 years ago (MS $>$ 10, $n = 43$) and age- and sex-matched control participants ($n = 40$). Ultrasound examinations were performed by two independent examiners. CCSVI criteria 1, 3, 4 and 5 as proposed by Zamboni were explored: (1) reflux in the internal jugular (IJV) and vertebral veins (VV), (3) IJV cross-sectional area (CSA) $\leq$0.3 cm^2, (4) absence of flow in IJV and VV, and (5) reverted postural control of venous outflow.

Results: Criteria 1, 4 and 5 were met in less than 10% of the MS patients and control participants as studied by both examiners. The level of inter-observer agreement was poor for all parameters except assessment of the CSA of IJV at the thyroid level. Findings meeting CCSVI criterion 3 (CSA $\leq$ 0.3 cm^2) were observed in 18/40 (45%) of the control participants, in 24/37 (65%) of MS $\leq$ 2 patients ($p = 0.09$ vs. control participants) and in 30/43 (70%) of the MS $>$ 10 patients ($p = 0.022$ vs. control participants).

Conclusions: The feasibility of the CCSVI criteria for common use is questionable because of low inter-observer agreement. Small-calibre IJVs meeting the CCSVI criterion 3 appear common in both Finnish control participants and MS patients, but the clinical significance of this finding is questionable.

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INTRODUCTION

Multiple sclerosis (MS) is largely considered to be an inflammatory disease. Damage to the myelin and axons of the brain and spinal cord is mediated by focal lymphocytic infiltration.[1] Zamboni et al. proposed that the pathophysiological mechanism of venous congestion as seen in the lower limbs (chronic venous insufficiency) is analogous to chronically impaired venous drainage from the central nervous system (CNS).[2–4] Common findings of the inflammatory chain in chronic venous insufficiency and MS have been reported to show some similarities.[2] Chronic impaired venous outflow from the CNS has been proposed to cause chronic cerebrospinal venous insufficiency (CCSVI). Zamboni et al. also suggested that multiple sclerosis (MS) may be caused by CCSVI,[5] and proposed five sonographic criteria for CCSVI. These include (1) reflux in the deep cerebral veins and/or internal jugular veins (IJV) and vertebral veins (VV), (2) reflux in deep cerebral veins, (3) stenosis of the IJVs, (4) missing flow in the IJVs and VVs, and (5) the lack of decrease

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in IJV diameter in the sitting position, that is so-called inverse postural control of the cerebral venous drainage.[5] Many studies have been devoted to confirming the CCSVI hypothesis, with contradictory results.[6–9] Some recent studies have suggested that CCSVI is likely to be a late secondary phenomenon.[10,11] The CCSVI hypothesis has generated extensive debate around the world.

Finland has a high incidence and prevalence of MS,[12,13] and this population is therefore well-suited for studying the risk factors for MS. The aim of the current study was to assess inter-observer agreement between two independent examiners as regards the sonographic criteria of CCSVI and to compare the ultrasound findings in Finnish MS patients at different stages of the disease with age- and sex-matched healthy control participants.

MATERIAL AND METHODS

Participants

Information concerning CCSVI was delivered to MS patients participating in an ad hoc meeting of the Finnish MS Society by two of the authors (PT, ML). On the same occasion, participants were informed of the present study, and volunteers to participate were recruited. During a 3-week recruitment period, 292 applications were received and 17 after the deadline (Fig. 1).

Consecutive patients living in the Hospital District of Helsinki and Uusimaa and meeting the inclusion criteria were enrolled according to a first-come-first-served principle (Fig. 1). All patients underwent a neurological examination and were informed about the study protocol, after which they signed an informed consent (PT, SA, MF). The inclusion criteria were: definite MS meeting the McDonald 2005 criteria and able to walk at least 20 metres without assistance (EDSS $<$ 6.5); age between 18 and 59 years and an MS diagnosis in the last 2 years or more than 10 years ago. The MS patients were divided into two groups: MS diagnosed no more than 2 years ago (MS $\leq$ 2) and MS diagnosed more than 10 years ago (MS $>$ 10). The female/male ratios in the MS groups were similar (3.1 and 3.8), and the MS $\leq$ 2 and MS $>$ 10 groups included 39 and 43 patients respectively. In addition, 40 age- and sex-matched healthy volunteer control participants were recruited (control group; Table 1). This study was approved by the ethics committee of the Hospital District of Helsinki and Uusimaa.

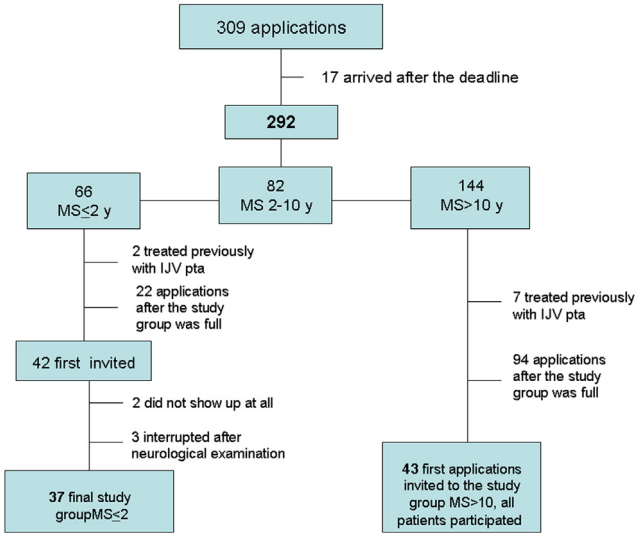

Figure 1. Flow chart of the patients. IJV = internal jugular vein; y = years.

Ultrasound examination

A total of 120 participants underwent an ultrasound examination; 37 patients in the group of MS $\leq$ 2, 43 patients MS $>$ 10 and 40 healthy control participants. Two out of 122 did not attend for ultrasound examination. All participants were examined by two independent examiners who were blinded to the participants' disease status and each other's findings. We aimed to ensure proper blinding by having the study nurse instruct the participants not to reveal their disease status during the ultrasound examination. The examiners were not in contact with each other during or after the examination. They were experienced in using the ultrasound systems. During a run-in period before the actual study, 15 participants (4 patients and 11 control participants who were not included in the actual study) were examined by the two examiners together to unify the assessment criteria of the duplex study. The first examination was always performed by a vascular surgeon (SL = first examiner), and immediately thereafter the examination was repeated in another room by a sonographer (TK = second examiner). Participants remained in the supine position for 3 minutes before the ultrasound examination. The examination was first performed with the patient lying in the supine position and then in a standard sitting position. The ultrasound equipment used was the GE Logiq E9 ultrasound system with a 9 MHz linear probe (SL) and the Toshiba Xario system with a 7.5 MHz linear probe (TK) and examiners used always the same ultrasound equipment. To test the repeatability of the area measurements between the two ultrasound equipments used in the current study, two examiners measured the area of carotid artery (eight measurements) so that the measurements were blinded from each other. There were no significant differences between the area measurements of carotid arteries between the two examiners.

The examination was performed following the criteria 1, 3, 4, and 5 suggested by Zamboni et al.: (1) reflux in the IJVs and/or VVs, (3) high-resolution B-mode evidence of IJV stenoses, (4) flow not Doppler-detectable in the IJVs and/or VVs, and (5) reverted postural control of the main cerebral venous outflow pathways.[3] Collapse of the IJV in upright position is physiologic effect. Reverted postural control measures the lack of collapse of the IJV in sitting position compared with supine position. We measured three different points in the IJV in the supine position – J1, J2 and J3 (Fig. 2). Intracranial assessment (Zamboni criterion 2) was not performed because of unavailability of ultrasound devices for intracranial examination.

Table 1. Demographic and clinical characteristics of multiple sclerosis (MS) patients and control participants.

	MS diagnosis ≤2 y	MS diagnosis >10 y	Control participants
No. of participants	39	43	40
Female/male (*n*)	28/9	34/9	30/10
Age, y, mean (range)	33.3 (20–59)	47.9 (32–58)	43.4 (24–62)
Mean duration, mo (range)	13.7 (3–24)	202.1 (120–348)	n.a.
EDSS, mean (range)	1.72 (0–5)	3.27 (0–6.5)	n.a.
Relapsing-remitting MS	37	32	n.a.
Secondary-progressive	0	10	n.a.
Primary progressive	2	1	n.a.
Disease-modifying treatment			
No current treatment	4	8	n.a.
Tysabri	9	1	n.a.
IFNB	20	17	n.a.
Copaxone	3	13[a]	n.a.
Immunosuppressive	2	5[a]	n.a.
Fingolimode	1	0	n.a.

EDSS = Expanded Disability Status Scale; IFNB = interferon beta; mo = months; y = years.
[a] One patient had both copaxone and immunosuppressive treatment.

Statistical analysis

Statistical analysis was carried out with partially unmasked data (MV). Continuous data are presented as mean values ± standard deviation, and proportions are presented as percentages. The statistical significance of cross-sectional area (CSA) measures between the examiners was tested using the dependent values *t*-test and, between the groups, the independent samples *t*-test with 95% CI. In the analysis of inter-observer agreement, a Bland-Altman plot was used for the CSA measures, and Cohen's kappa was applied when evaluating dichotomous variables. In comparison of the CSA between the study groups MS ≤ 2, MS > 10 and control participants, mean values by the two examiners were used. Dichotomous variables were compared using the chi-square test. Statistical evaluation was accomplished using SPSS 19.00 software (SPSS Inc., Chicago, IL, USA).

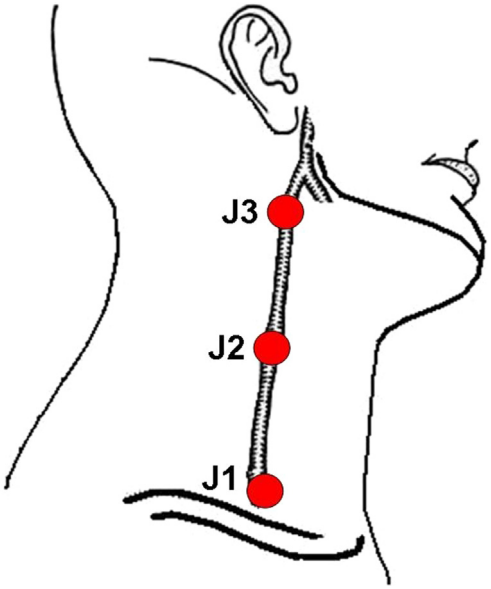

Figure 2. The three measurement points in the internal jugular vein.

RESULTS

Inter-observer agreement

Reflux in the IJVs and/or VVs in the supine and sitting position (Zamboni criterion 1). Reflux was very rare. The first examiner did not detect reflux in any participant. The second examiner detected reflux (>0.88 s) in two jugular veins, one in the control group and the other in the MS > 10 group.

High-resolution B-mode evidence of 'IJV stenosis' and measurement of the IJV area (Zamboni criterion 3). When the right and left IJVs of all participants were measured separately at any level in the vein applying the criterion of CSA ≤ 0.3 cm^2 for small-calibre veins, the first examiner found 52.5% of the right and 42.5% of the left veins to be of small calibre, whereas the second examiner found this criterion to be met in 60.8% and 50.0% of the right and left veins respectively. In 81.3% (195/240) of the participants, the examiners agreed on the finding (Cohen's kappa 0.67). At the level of J2, the area measurements did not differ significantly between the examiners, as they did at the other levels. In the Bland-Altman plot, the 95% limits of agreement at level J1, J2 and J3 were 0.55 cm^2, 0.49 cm^2 and 0.35 cm^2 respectively. In the sitting position, the 95% limits of agreement were 0.19 cm^2. When analysing the values of CSA ≤ 0.3 cm^2 at the level of J2, the 95% limits of agreement were 0.24 cm^2 (Fig. 3).

Flow not Doppler-detectable in the IJVs and/or VVs (Zamboni criterion 4). The first examiner detected absent IJV flow in the supine position in 5.4% (13/240) and the second examiner in 1.7% (4/240) of the participants. The Cohen's kappa between the examiners was 0.34. In the VV in the supine position, the first examiner detected no flow in 9.6% (23/240) and the second examiner in 3.8% (9/231) of the participants (Cohen's kappa 0.15). In the sitting position, absent flow in the IJV was seen in 8.6% (21/240) and 0.8% (2/240) of the participants by the first and second examiner respectively (Cohen's kappa 0.07). In the sitting

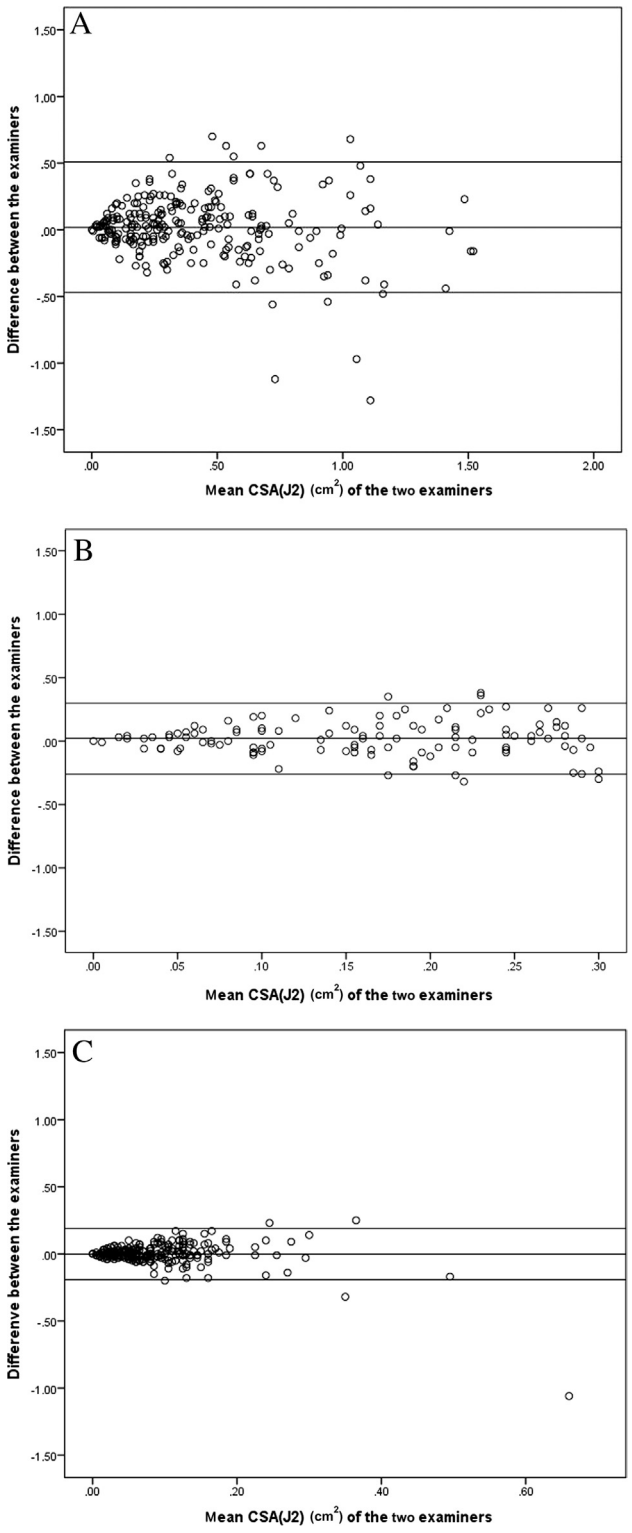

Figure 3. Bland-Altman plot on the measurements of cross-sectional area (CSA) at the level of J2 including all patients (A), patients with a mean CSA of $\leq$0.3 cm^2 (B), and as measured in the sitting position (C).

position, VV flow was absent in 5.0% (12/240) of the participants when examined by the first examiner, and in 8.3% (20/240) when examined by the second examiner, and only one of these absent flow cases coincided between the two examiners (Cohen's kappa 0.000).

Reverted postural control of the main cerebral venous outflow route measured in the IJV (Zamboni criterion 5). A negative value of Delta CSA (J2) supine–sitting in the IJV was found in 5.0% (12/240) of the participants by the first, and in 7.5% (18/240) of the participants by the second examiner, but in only three cases did both examiners arrive at a negative value (Cohen's kappa 0.15).

Differences between the study groups

The analysis of inter-observer agreement showed that the only reliable measure was the measurement of CSA at the level of J2 and the determination of IJV 'stenosis' CSA $\leq$ 0.3 cm^2 at the same level (Zamboni criterion 3). Therefore, the analysis on the differences between the three groups was performed using this criterion.

The mean CSA (J2) in the supine position was 0.37 $\pm$ 0.32 cm^2 in the MS $\leq$ 2 group, 0.36 $\pm$ 0.29 cm^2 in the MS $>$ 10 group and 0.52 $\pm$ 0.34 cm^2 in the control group. The following comparisons were made: MS $\leq$ 2 vs. MS $>$ 10 ($p = 0.6$), MS $\leq$ 2 vs. control ($p = 0.007$) and MS $>$ 10 vs. control ($p = 0.001$) (Fig. 4).

In the MS $\leq$ 2 and MS $>$ 10 group, CSA $\leq$ 0.3 cm^2 in one or both IJVs at the level of J2 was found in 65% (24/37) and 70% (30/43) (p = n.s.) of the patients, respectively, compared with 45% (18/40) in the control group ($p = 0.09$ in the comparison MS $\leq$ 2 vs. control participants and $p = 0.022$ in MS $>$ 10 vs. control participants). Bilateral CSA $\leq$ 0.3 cm^2 was found in 17/37 (46%) and 13/43 (30%) of the patients in the MS $\leq$ 2 and MS $>$ 10 groups, respectively, whereas the figure was 10/40 (25%) in the control group (Fig. 5). The following comparisons were made: MS $\leq$ 2 vs. control participants $p = 0.049$, MS $>$ 10 vs. control participants $p = 0.59$.

DISCUSSION

The role of venous congestion and chronic impaired venous outflow in the aetiology of multiple sclerosis is controversial. The first diagnostic tool to detect CCSVI is Doppler

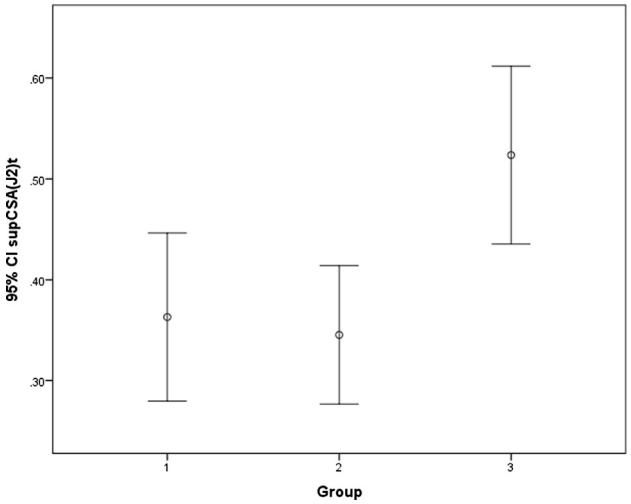

Figure 4. Mean cross-sectional area (CSA) at the level of J2 in the MS $\leq$ 2 group (1), MS $>$ 10 group (2) and control participants (3).

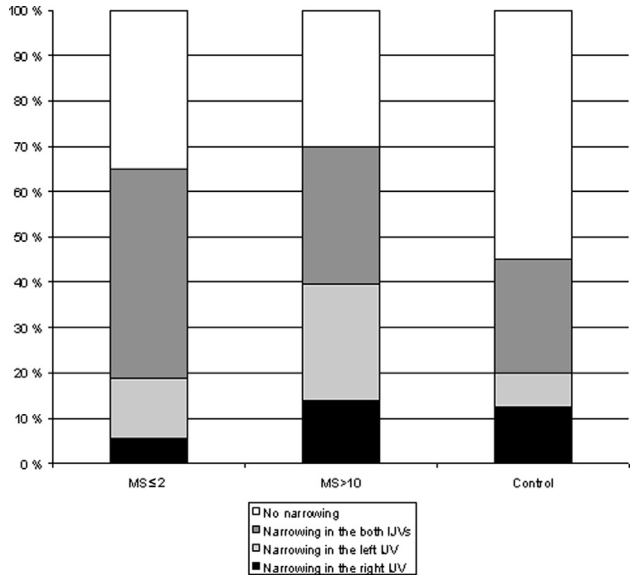

Figure 5. The prevalence of narrowing in the internal jugular vein (IJV) in the study groups.

duplex ultrasound, which provides an anatomic image and haemodynamic picture of the venous system. In the current study, we evaluated inter-observer agreement with regards to four out of the five proposed measures (Zamboni criteria 1, 3, 4 and 5) independently in a blinded fashion as established by two experienced examiners, both of whom were practised in the daily use of duplex sonography for more than 7 years.

The overall inter-observer agreement was poor for all parameters except the assessment of the CSA of the IJVs at the thyroid level where the ultrasound measurement was easy to perform. Related to the CSA, the detection of the proposed 'stenotic' IJV calibre (CSA $\leq$ 0.3 cm^2) also achieved high inter-observer agreement. In the comparisons between the study groups, we applied only those criteria that proved to be reliable and repeatable. We found that the calibre of the IJV was somewhat smaller in MS patients than in the control participants, and there was a slightly higher proportion of MS patients than control participants with a small-calibre IJV (CSA $\leq$ 0.3 cm^2). The frequency of such findings was so high in the control participants (45%) and the association with MS so weak that their clinical significance is highly doubtful.

Modern ultrasound equipment produces excellent B-mode images. The IJV was easy to detect from the images, and we encountered no problems in measuring the diameter from the B-mode images. At the level of J2, CSA both in sitting and supine positions was the most consistent parameter between the examiners. The thyroid level is easily approachable, and the measuring point is clear. The vein can be evaluated without compression. However, at the supraclavicular level, the detection of the vein as well as the diameter measurement proved more challenging, as shown by the wide limits of agreement at that level. In the inframandibular region, the limits of agreement were narrow, but there were significant differences between the examiners, suggesting a systematic difference in measurements. The second examiner systematically measured wider calibres at that level, suggesting a difference in the examination. It is unclear whether the first examiner compressed the vein with the ultrasound probe more heavily at this level where the vein lies deeper than, for example, at the thyroid level. These data illustrate the difficulty of repeating venous diameter measurements because of the low pressure of the vessel.

Menegatti et al. tested the reproducibility of Doppler ultrasound for screening CCSVI patients and assessed the variability between trained and non-trained observers.[14] After 1 month of scanning 15 participants, those not trained became as proficient as those who had been trained. Zivadinov et al. reported on intra-rater reproducibility in relation to disease status at baseline.[11] Twenty-eight participants were examined twice in a blinded manner over a 1-week period by the same examiner. The CCSVI status measured by ultrasound was interpreted as not similar in 3 out of 28 examinations.

In the CCSVI study in which Zamboni introduced the criteria, stenosis was assessed in high-resolution B-mode examinations of the cervical vessels.[5] A CSA value of $\leq$0.3 cm^2 was determined as the cut-off value by Zamboni.[5] This value was determined from the study by Lichtenstein et al. in a very different group of patients, 23% of whom had a CSA of $<$0.4 cm^2 in their jugular veins.[15] In the same year that Zamboni et al. introduced their CCSVI criteria, they published another criterion for measuring B-mode stenosis.[16] They determined venous stenosis as a reduction $>$50% in the CSA of the IJV. With this criterion, they found B-mode stenosis to be present in 28% of the MS patients and 0.6% of the control participants included in their population. In the current study, the threshold of 0.3 cm^2 was used. We suggest the use of different terminology and opt for the functionally neutral term 'small-calibre' IJV rather than 'stenosis.' In our material, patients with MS had a small-calibre IJV slightly more often than did control participants. However, the prevalence of small-calibre IJVs was also relatively high among healthy control participants, up to 45%, which is higher than in Zamboni's study where CSA $\leq$ 0.3 cm^2 was found in 37% of MS patients and in 0.4% of control participants. Zivadinov et al.[11] found B-mode values quite similar to our present study — 39% of healthy control participants and 64% of MS patients had a small-calibre IJV (Table 2).[5,11] Ultrasound has its limitations in the inframandibular segment as only magnetic imaging can assess the calibre at the jugular bulb level. Indeed, Doepp et al. observed by magnetic resonance venography that all of the IJV narrowings were located above the mandibular edge.[17] We are preparing a separate magnetic resonance venography analysis of our patients.

Reflux in the IJV was extremely rare in the current study, and our results are in accordance with the studies by Baracchini et al. and Mayer et al. in which no reflux was observed in the IJVs (Table 2).[6,9] Zamboni et al. found reflux in 77% of the MS patients and in none of the control

Table 2. Results of the present and previous studies.

Zamboni criteria	Baracchini 2011[6]	Doepp 2011[17]	Mayer 2011[9]	Zamboni 2006[2]	Zivadinov 2011[11]	Present study SL	Present study TK
Patients/control participants, *n*	50/110	56/20	20/20	109/132	310/163	80/40	80/40
Reflux IJV (%)	24/0	0/0	0/0	70/0	44/20	0/0	1/3
Reflux intracranial (%)	0/0	2/0	0/0	55/0	35/9	NA	NA
B-mode stenosis (%)	16/0	0/0	65/80	28/1	64/39	66/50	71/50
Flow not detectable (%)[a]	6/1	9/5	0/1	32/1	10/7	35/28	23/8
Reverted postural control (%)	16/5	7/15	0/0	56/16	11/7	5/13	18/3

IJV = internal jugular vein.
[a] IJV and/or vertebral vein in sitting or supine position.

participants.[5] Zivadinov et al. reported reflux in 45% and 20% of the patients and control participants respectively.[11] Measuring the reflux was described by Zamboni et al., and the cut-off value >0.88 was chosen from a functional and morphological study by Nedelmann et al.[18] Flow was assessed during a short period of apnoea following a normal exhalation, not a forced Valsalva manoeuvre.[5] Reflux also occurred in the sitting position, and the mechanism underlying this reflux differs from the reflux caused by the incompetence of the jugular valve.[5]

Limitations of the study

Although the two examiners were blinded as to which group the patient belonged to and patients with a severe walking disability were excluded at the time when patients were recruited to the study, two patients used assistance in walking at the time of the examination. In both cases, the disease duration exceeded 10 years. In our study, we were unable to assess transcranial Doppler. Therefore, only four out of five CCSVI criteria were measured. We also used two different ultrasound systems, which might have had some, presumably minor, influence on the results.

Conclusion

The present study indicates that the proposed CCSVI criteria 1, 4 and 5 are subject to marked inter-rater differences and are hence not feasible for common use, as was shown in the statement from the European Society of Neurosonology and Cerebral Hemodynamics.[19] The calibre of the IJV (CSA $\leq$ 0.3 cm^2, CCSVI criteria 3) proposed as the definition of 'stenosis' appears to be a common finding among Finnish MS patients and control participants. There were slightly more small-calibre IJVs in MS patients than in control participants, but the clinical significance of this finding is questionable.

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CONFLICT OF INTEREST

None.

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