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Magnetic Resonance Imaging of Internal Jugular Veins in Multiple Sclerosis: Interobserver Agreement and Comparison with Doppler Ultrasound Examination

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Background: Doppler ultrasound (US) has been widely used to evaluate the cervical venous system of multiple sclerosis patients according to the hypothesis of chronic cerebrospinal venous insufficiency with contradictory results. Venous anatomy and pathology can be examined with less operator-dependent magnetic resonance imaging (MRI). Our aim is to assess the interobserver agreement in measuring internal jugular vein (IJV) cross-sectional area (CSA) in MR images and to explore the agreement between US and MRI in the detection of calibers of $\leq$0.3 cm^2 in the IJV CSA in the prospective study.

Methods: Thirty-seven multiple sclerosis patients underwent MRI of the cervical venous system. Two independent neuroradiologists measured the CSA of IJV at the mid-thyroid level. Furthermore, the time from contrast enhancement of common carotid arteries to that of each IJV (transit time in seconds) was assessed, and recorded whether IJV or the vertebral plexus visualized first during the contrast passage. US examination had been performed earlier.

Results: Interobserver agreement for assessing IJV CSA in MR images was substantial: the measurements differed $>$0.5 cm^2 between the examiners in only 5 IJVs (7%), Cohen's kappa 0.79. Transit times from common carotid artery to IJV varied between 5.1 and 14.1 sec. Fifteen patients had left-to-right asymmetry in the speed of IJV contrast filling. IJV CSA $\leq$ 0.3 cm^2 was found in 51 IJVs on the basis of US. Ten of these IJVs (19.6%) showed IJV CSA $\leq$ 0.3 cm^2 also in MRI. All IJVs defined as CSA $\leq$ 0.3 cm^2 in MRI met this caliber criterion also in US.

Conclusions: Interobserver agreement at the thyroid level of the IJV was good at MRI measurements. The US defines more IJVs as narrow (CSA $\leq$ 0.3 cm^2) than MRI. The US measurements for IJV CSA are not comparable with these methods. The US seems too sensitive in terms of finding venous stenosis.

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INTRODUCTION

Chronic cerebrospinal venous insufficiency (CCSVI) hypothesis, proposed by Zamboni et al.,[1] has generated extensive debate around the world. It postulates stenotic neck vessels, venous reflux, and delayed emptying as a causative factor for multiple sclerosis (MS), possibly treatable by endovascular procedures.[1–3] Here, major confusion arises from the natural anatomic variability of the craniocervical venous system and a difficulty in imaging its structure and function reliably. A digital subtraction venography has been stated as a golden standard, but it is an invasive procedure and not without problems, when interpreting the results.[1–5] Noninvasive and more available Doppler ultrasound (US) has produced contradictory results.[1,6–8] It is highly operator dependent, and blinding for scientific studies can be difficult.[6,9–11] Our recent study assessed the interobserver agreement between 2 US examiners in applying the CCSVI criteria for MS patients.[1,9] The agreement was low for all other parameters except for measuring the cross-sectional area (CSA) of the internal jugular vein (IJV) at the level of the thyroid gland.[9]

Venous anatomy and pathology can be examined with magnetic resonance imaging (MRI). The MRI produces images readily assessable to independent readers. It also lacks operator-dependent problems inherent to US, such as the differing probe pressure on the low-pressure venous system by different examiners. The MRI methods applicable to image the cervical veins include time of flight (TOF), phase-contrast, and contrast-enhanced venography.[6,12–14] The current MRI methods do not allow the detection of brief venous reflux or small intraluminal structures, but they produce anatomical images where IJV CSA can be readily measured.

The imaging methods in previous MRI studies on the cervical venous system vary. These MRI methods have included contrast-enhanced anatomical imaging,[6,11,13,15] TOF imaging based on blood flow,[6,12] and phase-contrast measurements sensitive to flow direction.[11–13] A recent study compared TOF and contrast-enhanced MRI techniques. The contrast-enhanced technique appeared better than the TOF MR angiography (MRA) in depicting the vascular anatomy.[16] Only one previous study reports interobserver variability of IJV CSA measurements in MRI.[16]

Confusion prevails on how US and MRI correspond to each other in assessing IJV CSA ≤ 0.3 cm^2. A recent study comparing the 2 modalities has found MRI to be more sensitive in detecting small caliber IJVs.[15] Others have found good consistency between US and MRI, while others have found limited value of MRI in comparison with US, suggesting that MRI is less reliable in finding truly small caliber veins.[11,17]

Our aim is to assess interobserver agreement between 2 independent readers in measuring the IJV CSA in contrast-enhanced MR venography (MRV) and to explore the agreement of the IJV CSA measurements between US and MRI, with both methods assessed by 2 independent readers. We also included a dynamic MRA sequence to gain information on cervical venous flow dynamics and evaluate the relationship of flow dynamics and anatomy.

MATERIALS AND METHODS

Subjects

This prospective study was approved by the Ethics Committee of the Helsinki and Uusimaa healthcare district prospectively. The subjects (37 MS patients) participated in a previous study, where 80 MS patients and 40 healthy controls underwent US of the cervical veins by 2 independent operators.[9] We invited 40 MS patients from the population of that previous study for an MRI examination which was done 6 months after the US examination. Of them, 37 accepted the invitation and constituted the patient population for this study; the remaining 3 were reinvited but did not respond. The patients' demographic and clinical characteristics are shown in Table I.

Ultrasound Examination

The Doppler US examination and its results have been earlier described in detail.[9] All participants were examined by 2 independent examiners unaware to the subjects' disease status and each other's findings. The examination was performed following 4 of the 5 CCSVI criteria suggested by Zamboni et al.[1]: (1) reflux in the IJV and/or vertebral veins, (2) B-mode evidence of small caliber IJV (IJV CSA < 0.3 cm^2), (3) flow not detectable in the IJVs and/or vertebral veins, and (4) reverted postural control of the main cerebral venous outflow pathways. In that previous study, we found low agreement between the operators for all other parameters except for the IJV CSA assessment at the level of the thyroid gland.[9] In this study, the US measurement of IJV CSA at mid-thyroid level was compared with corresponding MRI measurement.

MRI Acquisition

The MRI data were acquired with a 3T scanner (MAGNETOM Verio; Siemens, Erlangen, Germany) and 8-channel head and neck coil. The imaging protocol included a contrast-enhanced T1-weighted 3D GRE

Table I. Demographic data and clinical characteristics of the MS patients

No. of subjects	37
Female/male (*n*)	28/9
Age, years, mean (range)	41.4 (23−59)
Mean duration, months (range)	111 (3−348)
EDSS, mean (range)	2.5 (0−6)
Relapsing-remitting MS	30
Secondary progressive MS	4
Primary progressive MS	3

EDSS, Expanded Disability Status Scale.[18]

sequence with spectral fat saturation (3D FLASH) and dynamic MRA (3D TWIST). The imaging volume for both sequences covered the neck and skull base from sternal notch to occiput in coronal plane.

For the dynamic MRA we inserted a venous line to the right antecubital vein and injected 10 mL of intravenous contrast (gadoterate meglumine 279.3 mg/mL) at 4 mL/sec, followed by a chaser bolus (20 mL NaCl at 4 mL/sec). Acquisition of 60 successive coronal volumes (1 volume/sec) begun simultaneously with contrast injection (time of repetition [TR] 3.08 msec, time of echo [TE] 1.13 msec, flip angle 20°, field of view [FOV] 300 mm, matrix 252 × 320, slice thickness 10 mm, sampling density of central k-space 15%, peripheral 25%, acceleration factor 2 for parallel imaging with GRAPPA technique). Each acquired volume was postprocessed to a single, coronal, maximum intensity projection image to produce a time series of contrast passage through systemic veins, cervical arteries, and skull base and cervical venous structures.

After the dynamic MRA, each patient received an additional dose of intravenous contrast up to their individual weigh-adjusted dose. High-resolution anatomical images were then acquired as a 3D FLASH volume with fat suppression (TR 4.23 msec, TE 1.51 msec, flip angle 18°, bandwidth 340 Hz/pixel, FOV 330 mm, matrix 420 × 448, in-plane resolution 0.8 × 0.8 mm^2, slice thickness 0.8 mm, interslice gap 0.16 mm, acquisition time [TA] 3.11 s). The isotropic acquisition with voxel size of 0.8 × 0.8 × 0.8 allowed later examining the image volume in any selected plane for IJV measurements.

MR Image Analysis

Two neuroradiologists (J.P. and J.N.) measured left and right IJV CSA in high-resolution anatomical images unaware to US measurement results and MRI measurement results of each other. They first identified the middle thyroid level; this was possible because the thyroid gland is well depicted in coronal nonsubtracted 3D FLASH images. They then manually measured each IJV CSA at that level. They also tried to detect if there was a site within the thyroid gland area where either IJV would be visibly narrower than it was at the exact middle thyroid level, and did an additional measurement at that level. They recorded table position coordinates for all measurements to enable later identification of the exact site of any measurement. The cutoff limit for small caliber IJV was the same as in the proposed CCSVI criteria (IJV CSA $\leq$ 0.3 cm^2).

One neuroradiologist (J.P.) recorded the contrast transit time (TT) from common carotid arteries to IJV, and whether vertebral plexus-vertebral vein system or the ipsilateral IJV visualized first during the dynamic MRA time series (3D TWIST). The TT was defined as the time from the first detectable contrast enhancement of common carotid arteries to the first detectable contrast enhancement of each IJV at the lowest third of the IJV. The speed of 3D TWIST image acquisition limited the temporal resolution of these measurements to 1 sec.

Statistical Analysis

Continuous data are presented as mean values ± standard deviation. The statistical significance of CSA measurements between the examiners were tested using the dependent values *t*-test. In the analysis of interobserver agreement and agreement between US and MRA, a Bland−Altman plot was used for the CSA measures. The statistical evaluation was accomplished using SPSS 19.00 software (SPSS, Inc., Chicago, IL).

RESULTS

Interobserver Agreement of MRI

For the IJV CSA measurements in MR images, the interobserver agreement was substantial: the measurements differed clearly between the examiners in 5 IJVs (7%), Cohen's kappa 0.787, $P < 0.001$. In Bland−Altman plot, 95% limit of agreement was 0.52 cm^2 (Fig. 1). In 4 of the 5 cases with significant difference in IJV CSA measurement, the readers had made the measurement at different level (difference in craniocaudal dimension 15−35.8 mm).

IJV CSA ≤ 0.3 cm^2 in MRI and Comparison of MRI and US

The IJV CSA at the level of mid-thyroid gland in MR images was $\leq$0.3 cm^2 in 10 of the 74 imaged IJVs (13%). The 10 IJVs with CSA $\leq$0.3 cm^2 occurred in 8 patients (21.6%), 6 with unilateral and 2 with bilateral IJV CSA $\leq$ 0.3 cm^2. Of those with unilateral

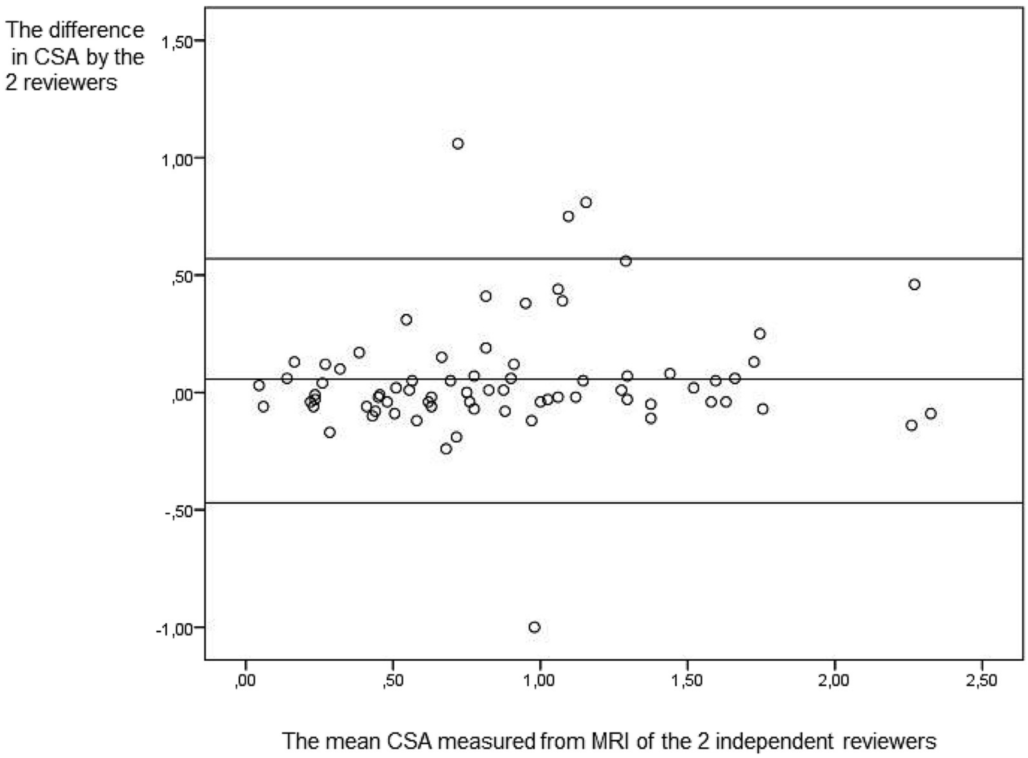

Fig. 1. Interobserver agreement between 2 neuroradiologists in MR images.

IJV CSA $\leq$0.3 cm^2, 3 were in the left and 3 in the right IJV. All 10 IJVs with CSA $\leq$ 0.3 cm^2 in MR images also had CSA $\leq$ 0.3 cm^2 in the US examination. There were 41 IJVs with CSA $\leq$ 0.3 cm^2 detected in US, but not in MRI. Thus, of the 51 IJVs with CSA $\leq$ 0.3 cm^2 in US, only 10 (19.6%) were scored concordantly with MRI. The IJV CSA at the level of mid-thyroid gland was systematically larger in MRI compared with that in US (Fig. 2).

TWIST Transit Times

The TTs from common carotid arteries to IJV varied between 5.1 and 14.1 sec (mean 8.4, standard deviation 2.2). Fifteen patients had left-to-right asymmetry in the speed of IJV contrast filling, with 1–4 s time difference of IJV contrast enhancement (Table II). In 1 patient, the left IJV only filled with contrast retrogradely; for her, no TT measurement was possible on that side. This patient had missing or hypoplastic ipsilateral transverse sinus. IJV was visualized before the vertebral plexus in 30 subjects (81%).

Relation of TWIST TT and IJV CSA ≤ 0.3 cm^2 in MR Images

The dynamic MRA (3D TWIST) TT asymmetry was found in 14 (38.9%) of the 36 eligible patients (1 excluded due to hypoplastic transverse sinus). Three of them had delayed TT and IJV CSA $\leq$ 0.3 cm^2 in the same side, 2 had bilateral IJV CSA $\leq$ 0.3 cm^2, and 9 did not have IJV CSA $\leq$ 0.3 cm^2 in either side. Considering the 6 patients with unilateral IJV CSA $\leq$ 0.3 cm^2, 3 had similar TWIST TT for both IJVs and 3 (patients 2, 8, and 15 in Table II) had 1–3 sec delay in the contrast filling in the same IJV that had CSA $\leq$ 0.3 cm^2.

DISCUSSION

As a noninvasive and widely available modality, the Doppler US examination has been the most common screening tool to analyze the structural and functional abnormalities according to the CCSVI hypothesis. The results are controversial: the US is strongly operator dependent, and flow measurements are challenging due to the low flow and pressure in the veins as well as the varying and often asymmetric anatomy of the venous system.[6,9] The interobserver agreement of US examination has been found to be remarkably low.[8–10] Taking all this into account, the US findings should be validated against other noninvasive methods.

The MRI is widely available and can produce structural images of the whole venous vasculature

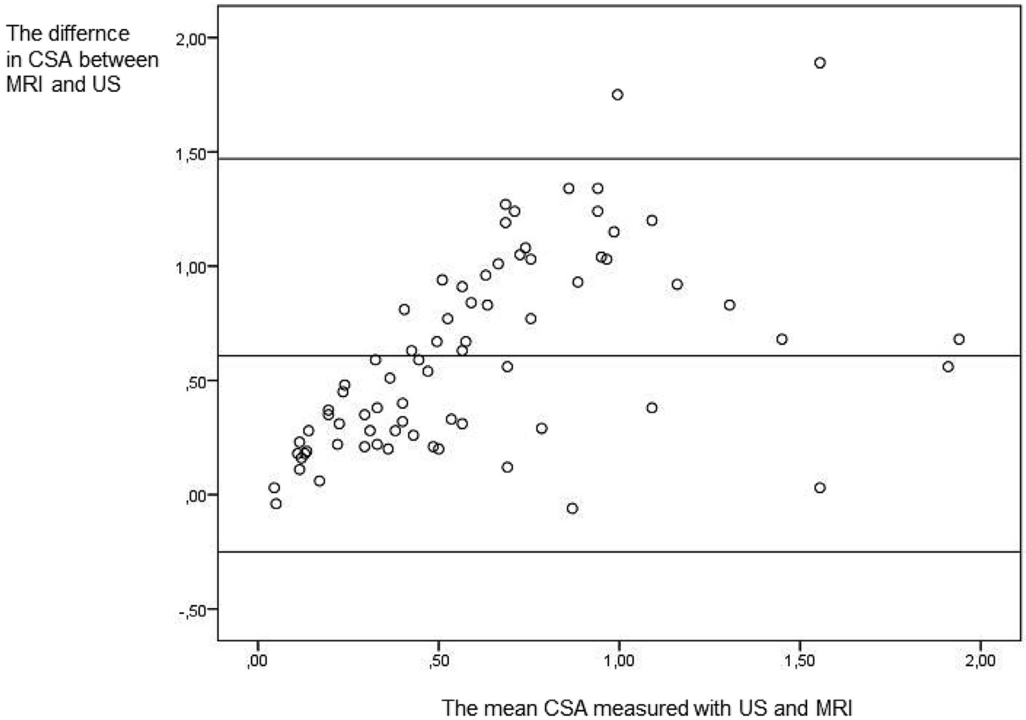

Fig. 2. Comparison of MRI and US.

Table II. Patients with 1–4 sec difference in TWIST transit time related to the MR and US findings

Patient	Transit time dx	Transit time sin	Transit time[a]	CSA MR dx	CSA MR sin	CSA US dx	CSA US sin	Vertebral plexus/ IJV[b]
1	8.1	12.1	4	2.5	0.75	0.61	0.63	No
2	13.2	10.2	3	0.03	0.38	0.07	0.07	Yes
3	11.1	8.1	3	0.06	0.2	0.03	0.02	No
4	5.1	8.1	3	1.33	0.38	0.09	0.01	No
5	10.1	12.2	2.1	1.27	0.46	0.24	0.26	No
6	10.1	8.1	2	0.74	1.47	0.11	0.43	Yes
7	9.1	11.1	2	1.61	0.52	0.27	0.24	No
8	7.1	9.1	2	0.6	0.23	0.2	0.04	No
9	10.1	8.3	1.8	0.98	1.32	0.04	0.05	No
10	7.1	8.1	1	1.48	0.81	0.45	0	No
11	11.1	12.1	1	0.23	0.28	0	0	Yes
12	6.1	7.1	1	1.17	0.56	0.16	0.3	No
13	11.1	12.1	1	0.45	0.44	0.17	0.22	Yes
14	13.1	14.1	1	0.74	0.4	0.2	0.19	No
15	10.1	11.1	1	0.33	0.17	0.11	0.06	Yes

dx, right; sin, left.
[a]The difference in TWIST transit time between left and right side (s).
[b]Vertebral plexus filling before IJV.

of the neck without the confounding effect of probe pressure. Brief retrograde flow during the cardiac cycle, thin venous flaps, and postural variations in venous drainage cannot, however, generally be assessed with the MRI. Therefore, a CCSVI criterion that is readily assessed with the MRI is the IJV CSA ≤ 0.3 cm^2. In this study, we aimed to assess how well the US and MRI measurements of the IJV CSA at the thyroid gland level of MS patients correspond to each other, and what is the level in interobserver variability in reading the IJV CSA in MR images.

Comparing our observed rate of the IJV CSA ≤ 0.3 cm^2 (10 of the 74 imaged IJVs, 13%) in the MRI with that of previous studies is complicated by the fact that different examiners have used very different definitions for the IJV CSA. Three studies apply a percent scale with the reference point set at bulbus jugular,[15] proximal IJV,[11] or not defined.[13] One study applies a morphological scale not used in any other studies,[6] and one reports ''stenosis'' (present or absent) without defining the stenosis criteria.[12] With these criteria, a small caliber IJV has been found with MRI in 0–70% of MS patients[6,11–13,15] and 21–42% of healthy controls.[6,11–13] In a recent study, Rahman et al.[16] compared 2 different MRV techniques (TOF and contrast-enhanced MRV) in assessing the extracranial vasculature in MS patients. The contrast-enhanced venography technique they employed is comparable with ours. They measured IJV CSA at 3 neck levels in 170 MS patients and 40 healthy controls. In their study, a stenotic CSA value differed from ours being <25 or <12.5 mm^2 depending on the neck level. Their observed prevalence of small caliber IJV in MS patients (55% and 61% depending on the technique used) is higher than ours (13%), despite the fact that our threshold for the small caliber IJV was greater, $\leq$0.3 cm^2 (or $\leq$30 mm^2). The difference may be attributable to that Rahman et al. measured IJV caliber in several different levels, and we measured only at the mid-thyroid level.

The interobserver agreement between the 2 experienced neuroradiologists was good in the IJV CSA measurement at the thyroid level: only 7% of the measurements were of 0.5 cm^2 limit. Recording the table position coordinates of each reading allowed examining the possible reasons for the disagreement. In 4 of the 5 cases with disagreement, the readers had made the measurement at different levels: only one category switch from IJV CSA $\leq$0.3 cm^2 to >0.3 cm^2. This contrasts with the markedly higher interobserver variability in measuring the IJV CSA at the mid-thyroid level of these same patients with US.[9]

The lower prevalence of the IJV CSA ≤ 0.3 cm^2 narrowing detected with MRI than with US in the same patient population was surprising.[9] All the patients who had the IJV CSA ≤ 0.3 cm^2 narrowing in the MRI also met that criterion in the US, but in addition there were 41 veins with the IJV CSA $\leq$ 0.3 cm^2 narrowing in the US but not meeting this criterion in MRI (Figs. 3 and 4). In our previous study, we examined the MS patients and healthy controls with US. The prevalence of IJV CSA $\leq$ 0.3 cm^2 was significantly higher among MS patients compared with healthy controls. In this study, the prevalence of IJV CSA ≤ 0.3 cm^2 was 5 times higher in US when compared with MRI. The reason behind this finding can only be suggested. One explanation may be that despite extremely careful and sensitive examination technique avoiding compression by all means, the US probe may cause some compression, and thus artifactually decrease the diameter of the IJV, and because IJV is an elliptical and pulsative vessel, it might play a role also, as well as possible extrinsic compression of omohyoid muscle (Fig. 4).[19,20] Also, the meaning of breathing variation is unknown. Dolic et al.[14] assessed the US and MRV in their study and found US to be more sensitive than MRV in detecting intraluminal changes in IJVs, whereas MRV was more sensitive in showing collaterals. Doepp et al.[15] reported MRV to be more sensitive to detect low caliber IJV compared with US. All but one of the low caliber IJVs were located above the mandibular edge which is not accessible by US. The only study with high degree of consistency between US and MRI findings is by Blinkenberg et al.[11]

The dynamic MR angiogram (TWIST) served in providing some information on how the narrowings observed in MRI affected the contrast flow. Two studies have previously applied a similar sequence with possibility to assess blood flow dynamics.[3,13] They, however, have weighed spatial resolution over temporal resolution. We found that even though one-third (n = 14, 38.9%) of the patients had asymmetrical contrast filling time of the IJVs, only 3 had an ipsilateral IJV CSA ≤ 0.3 cm^2. It seems apparent that not all IJVs with CSA ≤ 0.3 cm^2 significantly obstruct the flow. The venous drainage from the brain is markedly complex and has several alternative compensatory paths that contribute to the total flow.[21] Jugular veins are considered to be the main pathways. In our study, the dynamic MRA (TWIST) showed that IJVs were visualized before the vertebral venous system in 80% of the patients. The jugular and nonjugular pathways (mainly vertebral veins) anastomose extensively at the skull base level. They exhibit a high level of interindividual variability, and nonjugular pathways may function as a compensatory drainage mechanism.[13,16,21] It is thus very much debatable if small caliber of the IJVs can lead to venous congestion of the brain.

In this study, we measured and compared only the IJV narrowing which may due to hypoplasia or extrinsic muscle compression.[20] Recent studies postulated that CCSVI is mostly due to intraluminal obstacles or stuck valves and delayed emptying in the cerebral venous outflow.[3,22] MRI examination do not allow the detection of small intraluminar

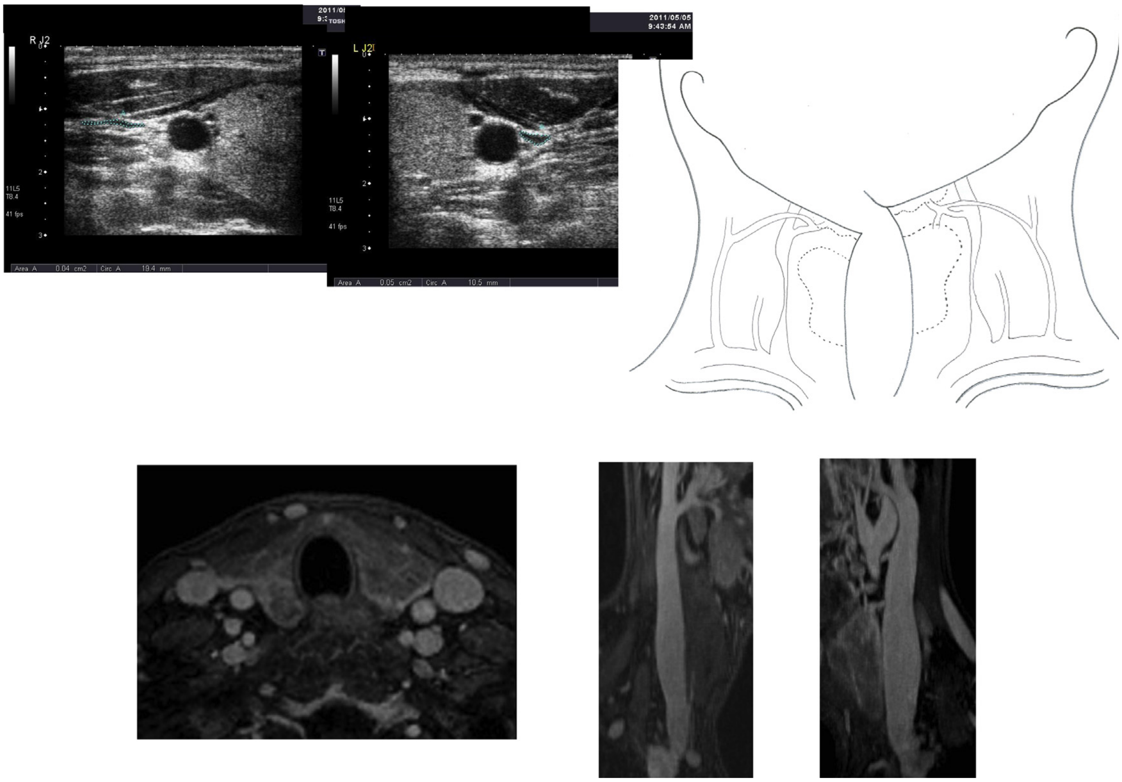

Fig. 3. Illustration of one MS patient with narrow internal jugular veins in ultrasound and drawings by sonographer Tomoko Kagayama and normal MRI findings in the same patient.

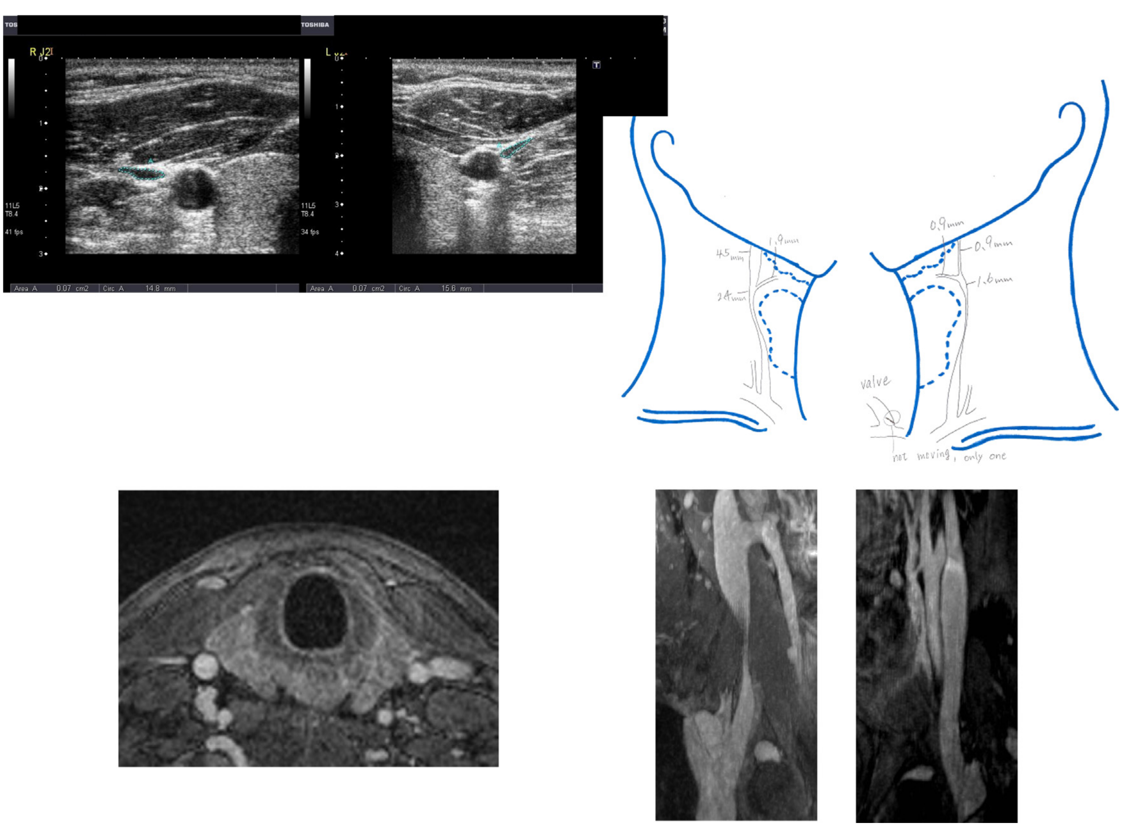

Fig. 4. Illustrations of one MS patient with narrow internal jugular veins both sides in ultrasound and drawings by Tomoko Kagayama and narrowing in the right side in MRI images, left normal.

structures. Malfunctioning of the valves could be detected by M-mode US.[23,24] Also, the IJV flow and delayed emptying might be detected by contrast-enhanced ultrasonography[25] or plethysmography.[26]

Limitations of the Study

As we aimed to produce measurements comparable with the previous US data on the same patients, we limited the IJV CSA measurements in MR images only to the mid-thyroid level.[9] Interobserver agreement was assessed only at the level of thyroid gland. The TT measurements are not validated against any other modality (digital subtraction angiology), and their temporal resolution is limited by the data acquisition time to 1 sec. It is thus possible that subtler TT differences would be detectable using methods with higher temporal resolution. Because this study utilized invasive methods (intravenous contrast agent), we did not examine healthy controls. Therefore, this study was not designed to test whether IJV CSA $\leq$ 0.3 cm^2 in MRI would be more prevalent among MS patients than among controls.

CONCLUSION

Interobserver agreement at the thyroid level of the IJV was good between 2 neuroradiologists at MRI measurements. When comparing the MRI and US, the US found 5 times more small caliber IJV narrowings than MRI. The MRI and US measurements for IJV CSA are not comparable. The US seems too sensitive in terms of finding venous stenosis—a possible explanation to be overdiagnosis of CCSVI.

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