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Use of neck magnetic resonance venography, Doppler sonography and selective venography for diagnosis of chronic cerebrospinal venous insufficiency. A pilot study in multiple sclerosis patients and healthy controls

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Abstract

Background: Chronic cerebrospinal venous insufficiency (CCSVI) is a vascular condition characterized by anomalies of primary veins outside the skull that restrict normal outflow of blood from the brain. CCSVI was recently described as highly prevalent in patients with multiple sclerosis (MS), and can be non-invasively diagnosed by Doppler sonography (DS) and invasively by selective venography (SV).

Objective: To investigate the value of neck magnetic resonance venography (MRV) for the diagnosis of CCSVI compared to DS and SV in patients with MS and in healthy controls (HC).

Methods: Ten MS patients and 7 HC underwent DS, 2D-Time-Of-Flight venography (TOF) and 3D-Time Resolved Imaging of Contrast Kinetics angiography (TRICKS). MS patients also underwent SV. The internal jugular veins (IJVs) and the vertebral veins (VVs) were assessed by both MRV sequences, and the findings were validated against SV and DS. SV has been considered the diagnostic gold standard for MS patients.

Results: All MS patients and none of the HC presented CCSVI, according to the DS criteria. This was confirmed by SV. For CCSVI diagnosis, DS showed sensitivity, specificity, accuracy, PPV and NPV of 100%, whereas the figures were 40%, 85%, 58%, 80% and 50% for 3D-TRICKS, and 30%, 85%, 52%, 75% and 46% for 2D-TOF in the IJVs. In MS patients, compared to SV, DS showed sensitivity, specificity, accuracy, PPV and NPV of 100%, 75%, 95%, 94% and 100%, whereas the figures were 31%, 100%, 45%, 100% and 26% for 3D-TRICKS and 25%, 100%, 40%, 100% and 25% for 2D-TOF in the IJVs.

Conclusion: The use of MRV for diagnosis of CCSVI in MS patients has limited value, and the findings should be interpreted with caution and confirmed by other imaging techniques such as DS and SV.

Introduction

Chronic cerebrospinal venous insufficiency (CCSVI) is a vascular condition characterized by anomalies of primary veins outside the skull that restrict the normal outflow of blood from the brain. [1] CCSVI was recently described as highly prevalent in patients with multiple sclerosis (MS), and can be diagnosed non-invasively using Doppler sonography (DS) and invasively using selective venography (SV). [1] Multiple stenoses of the principal pathways of extracranial venous drainage particularly affect the internal jugular veins (IJVs) and the azygous vein (AZY). In previous studies, by using SV and DS, Zamboni et al. showed that these stenoses define four main patterns of distribution associated with the opening of collaterals, very high incidence of reflux in both intracranial and extracranial venous segments, and loss of the postural regulation of cerebral venous outflow. [1, 2] Type A pattern is characterized by steno-obstruction of the proximal AZY associated with a closed stenosis of one of the two IJVs, where a reflux is always present in the stenosed IJV; type B pattern is characterized by bilateral stenoses of both IJVs and the proximal AZY where a reflux is present in all three venous segments; type C pattern is characterized by bilateral stenoses of both IJVs with a normal AZY system, where a reflux is present in the IJVs but not in the vertebral veins (VVs); type D pattern is characterized by multilevel involvement of the AZY and lumbar system where a reflux is present in the VVs.

Combined transcranial and extracranial echo-color-DS allows for non-invasive measurement of venous hemodynamic (VH) parameters indicative of CCSVI. [1] These VH parameters evaluate the presence of reflux in the IJVs and/or in the VVs in sitting and in supine positions, presence of reflux in the deep cerebral veins (DCVs), presence of B-mode anomaly and/or IJV stenosis, absence of the flow in IJVs and/or VVs, and presence of reverted postural control of the main cerebral venous outflow pathway by measuring the difference of the cross-sectional area of the IJVs in the supine

and upright positions. For a CCSVI diagnosis, at least 2 out of the 5 VH parameters need to be fulfilled. Two or more parameters in the same subject were never detected in controls, but perfectly overlapped with the diagnosis of clinically definite MS in previous studies. [1, 2] The diagnostic value of DS was validated against SV in previous studies, [1-3] and showed sensitivity of 100%, specificity of 100%, positive predictive value (PPV) of 100%, and negative predictive value (NPV) of 100%.

Magnetic resonance venography (MRV) is another non-invasive diagnostic tool that can depict, easily and globally, the venous system morphology of the head and neck. However, the value of this technique was not previously assessed for a diagnosis of CCSVI. Therefore, the objective of this pilot study was to preliminarily investigate the value of neck MRV for a diagnosis of CCSVI, compared to DS and SV, in patients with MS and in healthy controls (HC).

Methods

Subjects:

This cross-sectional study involved 10 consecutive relapsing-remitting (RR) MS patients diagnosed according to McDonald Criteria [4] and a group of 7 age- and sex-matched healthy controls (HC). The inclusion criteria were: RRMS, [5] an Expanded Disability Status Scale (EDSS), [6] between 0-5.5, age 18-65 years, disease duration between 5 and 10 years, being on treatment with current FDA-approved disease-modifying treatments and having normal renal function (creatinine clearance of >58 ml/min). Exclusion criteria included an acute relapse and/or steroid treatment within 30 days preceding study entry, pre-existing medical conditions associated with brain pathology (e.g., neurodegenerative disorder, positive history of alcohol abuse, etc.), and abnormal renal function. The study was approved by the local Institutional Review Committee.

Magnetic resonance venography:

All subjects were examined on a 3T GE Signa Excite HD 12.0 Twin Speed 8-channel scanner (General Electric, Milwaukee, WI), with a maximum slew rate of 150T/m/s and maximum gradient amplitude in each orthogonal plane of 50mT/m (zoom mode). A multi-channel head and neck (HDNV) coil manufactured by GE was used to acquire the following sequences: an enhanced and unenhanced 2D-Time-of-Flight (TOF) and 3D- Time Resolved Imaging of Contrast Kinetics (TRICKS) MRVs. The parameters used for 2D-TOF were: TR/TE 17/4.3 msec (repetition/echo time), flip angle of 70 degrees, 1.5 mm slice thickness, acquisition matrix 320/192 and acquisition in axial scan plane. The parameters used for 3D-TRICKS were: TR/TE 4.2/1.6 msec, flip angle of 30 degrees, 2 mm slice thickness, acquisition matrix 320/192 and acquisition in coronal scan plane. Intravenous gadolinium contrast was injected at a rate of 2ml/s using a pressure injector. The total volume of contrast was 20ml. The scan protocol consisted of 18 phases of acquisition, each of 5s duration.

The flow morphology of the IJVs was assessed on axial source images in unenhanced and enhanced 2D-TOF and on axial reconstructed 3D-TRICKS slices. The flow was considered in ordinal scale from absent (not visible flow) to ellipsoidal (patent lumen). Five qualitative flow categories were assigned: absent, pinpoint, flattened, crescentic and ellipsoidal. As the morphology of the IJV can vary along the vessel, we considered the narrowest point in both the inferior and the superior segments, respectively. Absent and pinpoint IJVs flow was considered abnormal. The VV flow was classified as visible or not visible.

We also assessed left and right asymmetries and prominence of the other most important visible veins in the neck such as the external jugular veins (EJVs), anterior jugular veins, jugular arch, facial veins, thyroid veins and deep cervical veins. The prominence was defined when the

diameter of those veins was higher then 5 mm in general, or higher than 7mm in the inferior segment of the EJV sinus that is often dilated.

All MRI scans were examined by two independent neuroradiologists in a blinded manner.

Unenhanced and enhanced 2D-TOF produced identical patterns and, therefore, for all comparisons with DS and SV we used unenhanced 2D-TOF.

The IJV MRV variable used for comparison with DS and SV was abnormal/normal flow, whereas the VV variable used for comparison with DS (VVs were not systematically evaluated with SV) was visible/non-visible flow. We considered comparing asymmetries and prominence of the other most important visible veins in the neck on MRV with DS and SV, but found it difficult to assess the differences without a specific predefined DS and SV assessment protocol, which was not part of this study.

Echo-color Doppler-sonography:

Cerebral venous return was examined using the echo-color DS (ECD Esaote-Biosound My lab 25) scanner equipped with 2.5 and 7.5-10 Mhz transducers, with the subject positioned on a bed tilted at 90 degrees and 0 degrees. All subjects were scanned following the established protocol for diagnosis of CCSVI, [1] consisting of transcranial and extracranial echo-DS to measure the 5 VH parameters indicative of CCSVI:

1- Reflux in the IJVs and/or in the VVs in sitting and in supine positions (90- 0 degrees). Reflux was defined as flow directed towards the brain for a duration of 0.88 s.

2- Reflux in the DCVs. Reflux was defined as reverse flow for a duration of 0.5 s in one of the DCV (internal cerebral vein, the basal vein of Rosenthal or the vein of Galen).

3- B-mode abnormalities or stenoses in IJVs. IJV stenosis was defined as a cross-sectional area of this vein inferior or equal to 0.3 cm^2. Flaps, webs, septums, etc., in the lumen of IJVs were considered B-mode abnormalities.

4- Flow that is not Doppler-detectable in IJVs and/or VVs despite multiple deep breaths.

5- Reverted postural control of the main cerebral venous outflow pathway by measuring the difference in the cross-sectional area of the IJVs in the supine and upright positions.

DS was examined by an expert technologist in a blinded manner. Presence of at least one of the following IJVs VH anomalies was considered an abnormal exam: B-mode abnormalities (flaps, septums, web), stenoses, absence of detectable flow, and presence of reflux in both sitting and supine positions. Absence of detectable flow (called block) in VVs was considered abnormal. DS abnormal/normal IJVs and VVs parameters were used for comparison with MRV and SV.

Venography:

SV was performed only in MS patients after the DS examination showed that all MS patients fulfilled ≥2 VH criteria. [1] SV was performed via catheterization of the left iliac femoral vein and comprised visualization of lumbar veins, left renal vein, AZY vein and IJVs. [2] Significant stenosis was considered to be any venous lumen reduction greater than 50%. We investigated the following anomalies (Table 1): annulus - significant circumferential stenosis of the venous wall; septum/valve malformation - anomalous valve apparatus causing significant flow obstacles at the level of the junction of the brachiocepahlic trunk; hypoplasia - under-developed, long venous segment; twisting - severe stenosis due to a twisted venous segment; membranous obstruction - a membrane almost occluding a vein; agenesis - complete anatomical absence of a venous segment.

SV was conducted by an interventional radiologist. Presence of at least one of these anomalies in IJVs and VV was considered an abnormal exam. SV was used as a gold standard for comparison with MRV and DS.

Statistical analysis:

We calculated the sensitivity, specificity, accuracy, PPV and NPV and their relative confidence intervals (CI) for various diagnostic methods. The sensitivity was calculated as: true-positive / [true-positive+false-negative], the specificity as: true-negative / [true-negative+false-positive], the accuracy as: [true-positive+true-negative] / [true-positive+false-negative+true-negative+false-positive], the PPV as: true-positive / [true-positive + false positive] and the NPV as: true-negative / [true-negative+false-negative].

For CCSVI diagnostic comparison between MS patients and HC we calculated sensitivity, specificity, accuracy, PPV and NPV for DS and MRV. True-positive was defined as an abnormal imaging finding on 3D-TRICKS, 2D-TOF and DS in presence of MS diagnosis, false-positive as an abnormal imaging finding in the absence of MS diagnosis, false-negative as a normal imaging finding in presence of MS diagnosis, and true-negative as a normal imaging finding in the absence of MS diagnosis.

By considering the SV findings in right and left IJV as a gold standard, we calculated the sensitivity, specificity, accuracy, PPV and NPV for 3D-TRICKS, 2D-TOF and the DS for left and right IJVs. The true-positive was defined as an abnormal imaging finding on 3D-TRICKS, 2D-TOF or DS and presence of abnormal IJV on SV, false-positive as an abnormal imaging finding on those techniques in the absence of abnormality on SV, false-negative as a normal imaging finding and the presence of abnormality on SV, and true-negative as a normal imaging finding in the absence of abnormality on SV.

Results

Demographic and clinical characteristics:

The mean age of the MS patients was 36.4 years (SD 7.3), mean disease duration 8.4 years (SD 1.8) and median EDSS 2.5. Seventy percent of the MS patients were females. The proportion of females to males ($p = 0.69$, Fisher Exact test) and the mean age of the two groups ($p = 0.559$) were similar. All MS patients were on disease-modifying therapy (three were on subcutaneous interferon-beta 1a, two on intramuscular interferon-beta 1a, three were on natalizumab and two were on glatiramer acetate).

Comparison between multiple sclerosis patients and healthy controls:

Table 1 shows DS results in MS patients and HC, and the SV findings in MS patients. All MS patients and none of the HC presented CCSVI according to the DS criteria. The mean number of DS VH criteria was 4.2 (SD 0.8) in MS and 0.2 (SD 0.4) in HC ($p<0.001$). DS, MRV and SV abnormality findings for the left and right IJVs in MS patients and HC are shown in Table 2. For CCSVI diagnosis, DS showed a sensitivity, specificity, accuracy, PPV and NPV of 100%, whereas the figures were 40%, 85%, 58%, 80% and 50% for 3D-TRICKS, and 30%, 85%, 52%, 75% and 46% for 2D-TOF in the IJVs (Table 3).

Comparison between magnetic resonance venography, Doppler sonography and selective venography in multiple sclerosis patients:

The sensitivity, specificity, accuracy, PPV and NPV for 3D-TRICKS to detect IJVs abnormalities on SV were 31%, 100%, 45%, 100% and 26% and 25%, 100%, 40%, 100% and 25% for 2D-TOF (Table 4). The DS figures were 100%, 75%, 95%, 94% and 100%, respectively. We detected flow in all VVs explored by MRV. There were 2 MS patients who showed blockage of the VVs in DS without correlation with MRV, where vertebral flow was visualized.

In 57.1% (4/7) of the HC there was no overlap between MRV and DS findings. In 42.8% (3/7) of the HC, MRV showed variability in the morphology of the IJVs between both sequences (Table 2 and Figures 1 and 2). In 70% (7/10) of MS patients there was no overlap between MRV and DS findings (Figures 3-5). In 60% (6/10) of MS patients, MRV showed variability in the morphology of the IJVs between both techniques (Figure 6).

A flattened segment of IJVs was detected in 90% (9/10) of MS patients and 85% (6/7) of the HC in both MRV sequences (Table 5 and Figures 7-8).

Discussion

This pilot study investigated the value of neck MRV for a diagnosis of CCSVI compared to DS and SV in MS patients and in HC. For CCSVI diagnosis, DS showed higher sensitivity, specificity, accuracy, PPV and NPV in the IJVs, compared to 3D-TRICKS and 2D-TOF. In MS patients, compared to SV, DS showed higher sensitivity, specificity, accuracy, PPV and NPV compared to 3D-TRICKS and 2D-TOF. These findings indicate that MRV has limited value for diagnosis of CCSVI, despite being an excellent tool for depicting the morphology of the head and neck venous system and being less operator-dependent and less time-consuming than DS. The reasons for this limitation are mainly due to a lack of MRV dynamism in real-time, a lower resolution than DS and SV and the nature of the veins themselves, which are prone to morphological and haemodynamic changes under various circumstances.

In contrast to arteries, veins have a tendency to collapse and their morphology and size can change along the vessel length depending on hydration status, position (gravitational variability), intrathoracic pressure (respiration, Valsalva), cardiac status and compression from adjacent structures. [7-10] This can explain why we found a significant variability in the morphology of the IJVs between 2D-TOF and 3D-TRICKS in 43% of the HC and 60% of MS patients, which cannot be

attributed to the technical differences per se, nor to the presence or absence of contrast enhancement (no differences were found between unenhanced and enhanced 2D-TOF). In the supine position (necessary for MRV examination), morphological changes in the veins could be affected by different respiratory phases during the sequence acquisition, different positioning of the head and neck coil, changes in the contact points (extrinsic compression) with the coil or changes due to swallowing movements. Also, it has been described a physiologic stenosis of the left brachiocephalic vein during regular breathing in the supine position, which can cause retrograde flow as well as venous stasis in the left IJV and left sigmoid sinus. [11-15]

There are also technical differences which can explain some of the variations between the 2D-TOF and 3D-TRICKS, mainly due to the use of contrast in the 3D-TRICKS. Techniques using contrast depict the vessels better, especially at points with decreased or slow flow; they are less susceptible to flow related artifacts (Figures 1 and 6). The maximum intensity projection (MIP) volumetric reconstructions of those sequences often underestimate the vascular caliber, especially when there are segments with decreased flow (velocity or volume). [16] For this reason, pinpoint, flattened or even some crescentic segments visualized on the source images appear to be absent on these volumetric reconstructions (Figures 7 and 8). In the subjects that we analyzed, there were two quite common points of narrowing/flattening in the jugular veins; one was at the level of the lateral masses of the atlas, and the other at the thyroid gland level (Figures 6 and 7). We did not consider flattening as a pathological finding because it had the same appearance and approximate frequency in HC and in MS patients (Table 5).

In relation to these technical flow-related limitations, we noted a great physiological variance of the jugular drainage fraction in the supine position, [9, 17] which can explain the reduced caliber of the IJV in some subjects in this position and consequently in MRVs. Doepp et al. [9] described

different cerebral drainage patterns in the horizontal position in healthy subjects: a) a predominant jugular-drainage, which was present in 72% of all individuals, b) a balanced jugular/extrajugular drainage present in 22% of the subjects and c) a predominant extrajugular drainage in 6% of the subjects, also called "neck-drainers and/or spinal-drainers."

Most of the diagnostic parameters for CCSVI such as reflux, intraluminal abnormalities (annulus, flap, web, septum, membrane, malformed valve) or dynamic postural control exploration, are easily assessed with high-resolution DS [1] but cannot be explored with MRV. For the 2D-TOF we did not use a saturation pulse, so the arterial and venous systems were depicted simultaneously, and consequently an assessment of reflux was not possible. For the 3D-TRICKS, it was possible to register some subjects with visible venous reflux on the same side of the contrast injection but usually there were multiple artifacts over the area (thoracic inlet) that made impossible the correct assessment of this variable. The MRV techniques do not have enough resolution to show vessel wall or intraluminal abnormalities such as annulus, webs, flaps, webs, etc., in contrast to high-resolution DS and SV. This was one of the main limits in creating the abnormality assignments for 2D-TOF and 3D-TRICKS that decreased their sensitivity, specificity, accuracy, PPV and NPV for CCSVI diagnosis. In 70% of MS patients and 57.1% of HC, MRV and DS did not show any overlap between the findings on both examinations (Table 2, Figures 2 and 5).

Although venous collateral circulation in the necks of MS patients was previously described as a compensatory mechanism of CCSVI, [1, 2] we were not able to compare the findings between the three diagnostic methods, as our original DS and SV protocols did not systematically evaluate asymmetries and prominence. The comparison of neck vein asymmetry and prominence between MS patients and HC on MRV was beyond the scope of this study and will be the subject of future investigation on a larger sample of subjects.

Our study has several limitations. The first one is the low number of subjects. The second is the use of independent professionals for reading of DS, MRV and SV. However, despite these limits, we obtained preliminary findings that can be useful in future diagnostic CCSVI studies, as there is at the moment a lack of experience with the use of MRV for diagnosis of CCSVI. Another limitation of the study is that we compared only IJVs and VVs between the three diagnostic methods. In previous studies, [1, 2] it was shown that AZY vein malformations, characterized mainly by membrane obstructions and twisting, are frequently present and significantly contribute to diagnosis of CCSVI. During the development of the MRV protocol, we tried to image the AZY vein, but the quality of the protocol was very low and did not reliably assess the morphology of the AZY vein, mostly because we did not use cardiac gating and the fields of view were centered on the neck. Therefore, the diagnostic value of MRV for assessment of the AZY vein needs further technical improvement.

This pilot study showed that MRV has limited value for diagnosing CCSVI. The MRV data should be interpreted with caution and the findings must be confirmed by other imaging techniques such as DS and SV.

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Table Legends:

Table 1: MS – multiple sclerosis; HC – healthy control; IJV –internal jugular vein; AZY – azygous vein: CCSVI - Chronic cerebrospinal venous insufficiency; Selective Venography patterns: Type A pattern is characterized by steno-obstruction of the proximal AZY associated with a closed stenosis of one of the two IJVs, where a reflux is always present in the stenosed IJV; type B pattern is characterized by bilateral stenoses of both IJVs and the proximal AZY, where a reflux is present in all three venous segments; type C pattern is characterized by bilateral stenoses of both IJVs with a normal AZY system, where a reflux is present in the IJVs but not in the vertebral veins (VVs); type D pattern is characterized by multilevel involvement of the AZY and lumbar system, where a reflux is present in the VVs.

Table 2: MS – multiple sclerosis; HC – healthy control; RIJV – right internal jugular vein; LIJV – left internal jugular vein; 2D-TOF– 2D-Time-of-Flight venography; 3D-TRICKS – 3D- Time Resolved Imaging of Contrast Kinetics venography; not perf –Not performed

Table 3: DS–Doppler sonography; 2D-TOF– 2D-Time-of-Flight venography; 3D-TRICKS – 3D-Time Resolved Imaging of Contrast Kinetics venography; PPV–positive predictive value; NPV–negative predictive value; CI–confidence interval

Table 4: DS–Doppler sonography; 2D-TOF– 2D-Time-of-Flight venography; 3D-TRICKS – 3D-Time Resolved Imaging of Contrast Kinetics venography; PPV–positive predictive value; NPV–negative predictive value; CI–confidence interval

Table 5: MS – multiple sclerosis; HC – healthy control s – superior segment; i – inferior segment; RIJV - right internal jugular vein; LIJV: left internal jugular vein; F - flattened; NoF - non flattened

Figure legends:

Figure 1. Variability between the right internal jugular vein displayed on axial 2D-TOF (a) and axial 3D-TRICKS (b) (arrows) in a healthy control. 3D-TRICKS depicted the vein better at point with decreased flow.

Figure 2. Healthy control showing right internal jugular vein pinpoint/absent flow on axial 2D-TOF (a) and absent flow on axial (b) and volumetrically reconstructed (c) 3D-TRICKS. No Doppler sonography (d) abnormalities were detected in the right internal jugular vein.

Figure 3. Good overlap between narrowing of left internal jugular veins on axial 2D-TOF (a), axial (b) and volumetrically reconstructed (c) 3D-TRICKS and Doppler sonography (d) in multiple sclerosis patient. All three techniques showed similar findings in left internal jugular vein.

Figure 4. 3D-TRICKS (a) shows normal left internal jugular vein, whereas selective venography (b) shows stenosis in patient with multiple sclerosis. Selective venography shows normal right internal jugular vein (c).

Figure 5. 3D-TRICKS (a) shows normal internal jugular veins in MS patient, whereas selective venography shows bilateral internal jugular vein abnormalities characterized by a septum in the right internal jugular vein (b) and an annulus in the left internal jugular vein (c). Doppler sonography confirmed selective venography findings.

Figure 6. Variability between the left internal jugular vein displayed on axial 2D-TOF (a) and axial 3D-TRICKS (b) (arrows) in patient with multiple sclerosis. 2D-TOF showed absent and 3D-TRICKS showed ellipsoidal flow at the same point.

Figure 7. Example of flattening of right internal jugular vein on axial 2D-TOF (a), axial (b) and volumetrically reconstructed (c) 3D-TRICKS in a healthy control. Doppler sonography (d) showed normal examination.

Figure 8. Example of bilateral flattening of internal jugular veins on axial 2D-TOF (a), axial (b) and volumetrically reconstructed (c) 3D-TRICKS in a healthy control. Doppler sonography (d and e) showed normal examinations.

Table 1: Doppler sonography and selective venography findings in multiple sclerosis patients and healthy controls.

	Doppler Pattern	Selective Venography	CCSVI Selective Venography Pattern	IJV right finding	IJV left finding	AZY finding	Lumbar vein finding
MS1	abnormal	abnormal	A	normal	annulus	membrane	normal
MS2	abnormal	abnormal	C	septum	annulus	normal	normal
MS3	abnormal	abnormal	C	annulus	septum	normal	normal
MS4	abnormal	abnormal	A	normal	annulus	kinking	normal
MS5	abnormal	abnormal	A	annulus	normal	membrane	normal
MS6	abnormal	abnormal	B	annulus	septum	membrane	normal
MS7	abnormal	abnormal	D	normal	annulus	normal	dilatation
MS8	abnormal	abnormal	C	annulus	malformed valve	normal	normal
MS9	abnormal	abnormal	B	septum	annulus	membrane	normal
MS10	abnormal	abnormal	B	septum	annulus	membrane	normal
HC1	normal	not performed	not performed	not performed	not performed	not performed	not performed
HC2	normal	not performed	not performed	not performed	not performed	not performed	not performed
HC3	normal	not performed	not performed	not performed	not performed	not performed	not performed
HC4	normal	not performed	not performed	not performed	not performed	not performed	not performed
HC5	normal	not performed	not performed	not performed	not performed	not performed	not performed
HC6	normal	not performed	not performed	not performed	not performed	not performed	not performed
HC7	normal	not performed	not performed	not performed	not performed	not performed	not performed

Table 2: Comparison between Doppler sonography, magnetic resonance venography and selective venography findings of the internal jugular veins in patients with multiple sclerosis and in healthy controls.

	2D-TOF		3D-TRICKS		Doppler Sonography		Selective Venography	
	RIJV	LIJV	RIJV	LIJV	RIJV	LIJV	RIJV	LIJV
MS1	**normal**	**normal**	**normal**	abnormal	abnormal	abnormal	**normal**	abnormal
MS2	**normal**	**normal**	abnormal	abnormal	abnormal	abnormal	abnormal	abnormal
MS3	**normal**	**normal**	**normal**	**normal**	abnormal	abnormal	abnormal	abnormal
MS4	**normal**	**normal**	**normal**	**normal**	**normal**	abnormal	**normal**	abnormal
MS5	**normal**	**normal**	**normal**	**normal**	abnormal	**normal**	abnormal	**normal**
MS6	**normal**	**normal**	**normal**	**normal**	abnormal	abnormal	abnormal	abnormal
MS7	**normal**	abnormal	**normal**	abnormal	**normal**	abnormal	**normal**	abnormal
MS8	abnormal	abnormal	abnormal	**normal**	abnormal	abnormal	abnormal	abnormal
MS9	**normal**	abnormal	**normal**	**normal**	abnormal	abnormal	abnormal	abnormal
MS10	**normal**	**normal**	**normal**	**normal**	abnormal	abnormal	abnormal	abnormal
HC1	**normal**	**normal**	**normal**	**normal**	**normal**	**normal**	not perf.	not perf.
HC2	**normal**	**normal**	**normal**	**normal**	**normal**	**normal**	not perf.	not perf.
HC3	**normal**	**normal**	**normal**	**normal**	**normal**	**normal**	not perf.	not perf.
HC4	**normal**	**normal**	**normal**	**normal**	**normal**	abnormal	not perf.	not perf.
HC5	abnormal	**normal**	abnormal	**normal**	**normal**	abnormal	not perf.	not perf.
HC6	**normal**	**normal**	**normal**	**normal**	**normal**	abnormal	not perf.	not perf.
HC7	**normal**	**normal**	**normal**	**normal**	**normal**	abnormal	not perf.	not perf.

Table 3. Sensitivity, specificity, accuracy, positive predictive and negative predictive value for Doppler sonography and magnetic resonance venography in relation to CCSVI diagnosis for detection of internal jugular vein abnormalities between MS patients and healthy controls.

	Sensitivity % (95% CI)	Specificity % (95% CI)	Accuracy % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
DS	100 (72.2 – 100)	100 (64.5 – 100)	100 (81.5 – 100)	100 (72.2 – 100)	100 (64.5 – 100)
2D-TOF	30 (10.7– 60.3)	85 (48.6 – 97.4)	52 (30.9 – 73.8)	75 (30.0 – 95.4)	46 (23.2 – 70.8)
3D-TRICKS	40 (16.8 – 68.7)	85 (48.6 – 97.4)	58 (36.0 – 78.3)	80 (37.5 – 96.3)	50 (25.3 – 74.6)

Table 4: Sensitivity, specificity, accuracy, positive predictive and negative predictive value of Doppler sonography and magnetic resonance venography in relation to selective venography (gold standard) for detection of internal jugular vein abnormalities.

	Sensitivity % (95% CI)	Specificity % (95% CI)	Accuracy % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
DS	100 (80.6-100)	75 (30.0-95.4)	95 (76.3-99.1)	94 (73.0-98.9)	100 (43.8-100)
2D-TOF	25 (10.1-49.5)	100 (51.0-100)	40 (21.8-61.3)	100 (51.0-100)	25 (10.1-49.5)
3D-TRICKS	31 (14.1-55.6)	100 (51.0-100)	45 (25.8-65.7)	100 (56.5-100)	26 (10.9-51.9)

Table 5. Variability of the morphology of the internal jugular veins in healthy controls and multiple sclerosis patients for 3D-TRICKS versus 2D-TOF in relation to flattening.

	2D-TOF				3D-TRICKS			
	sRIJV	sLIJV	iRIJV	iLIJV	sRIJV	sLIJV	iRIJV	iLIJV
MS1	NoF	NoF	**F**	**F**	NoF	**F**	**F**	NoF
MS2	NoF	NoF	**F**	NoF	NoF	NoF	NoF	NoF
MS3	NoF	NoF	**F**	NoF	NoF	NoF	**F**	NoF
MS4	NoF	NoF	NoF	NoF	**F**	NoF	NoF	NoF
MS5	NoF	NoF	NoF	NoF	NoF	NoF	NoF	NoF
MS6	NoF	**F**	NoF	NoF	**F**	**F**	NoF	NoF
MS7	NoF	NoF	NoF	NoF	NoF	NoF	**F**	NoF
MS8	NoF	NoF	NoF	NoF	**F**	NoF	NoF	NoF
MS9	NoF	NoF	**F**	NoF	NoF	NoF	**F**	**F**
MS10	NoF	NoF	**F**	NoF	NoF	NoF	**F**	NoF
HC1	NoF	**F**	NoF	NoF	NoF	NoF	NoF	NoF
HC2	NoF	**F**	NoF	NoF	NoF	**F**	NoF	NoF
HC3	NoF	NoF	**F**	NoF	NoF	NoF	**F**	NoF
HC4	NoF	NoF	**F**	**F**	NoF	NoF	**F**	**F**
HC5	NoF	NoF	NoF	NoF	NoF	NoF	NoF	NoF
HC6	**F**	**F**	NoF	NoF	**F**	**F**	NoF	NoF
HC7	**F**	**F**	NoF	NoF	**F**	**F**	NoF	NoF

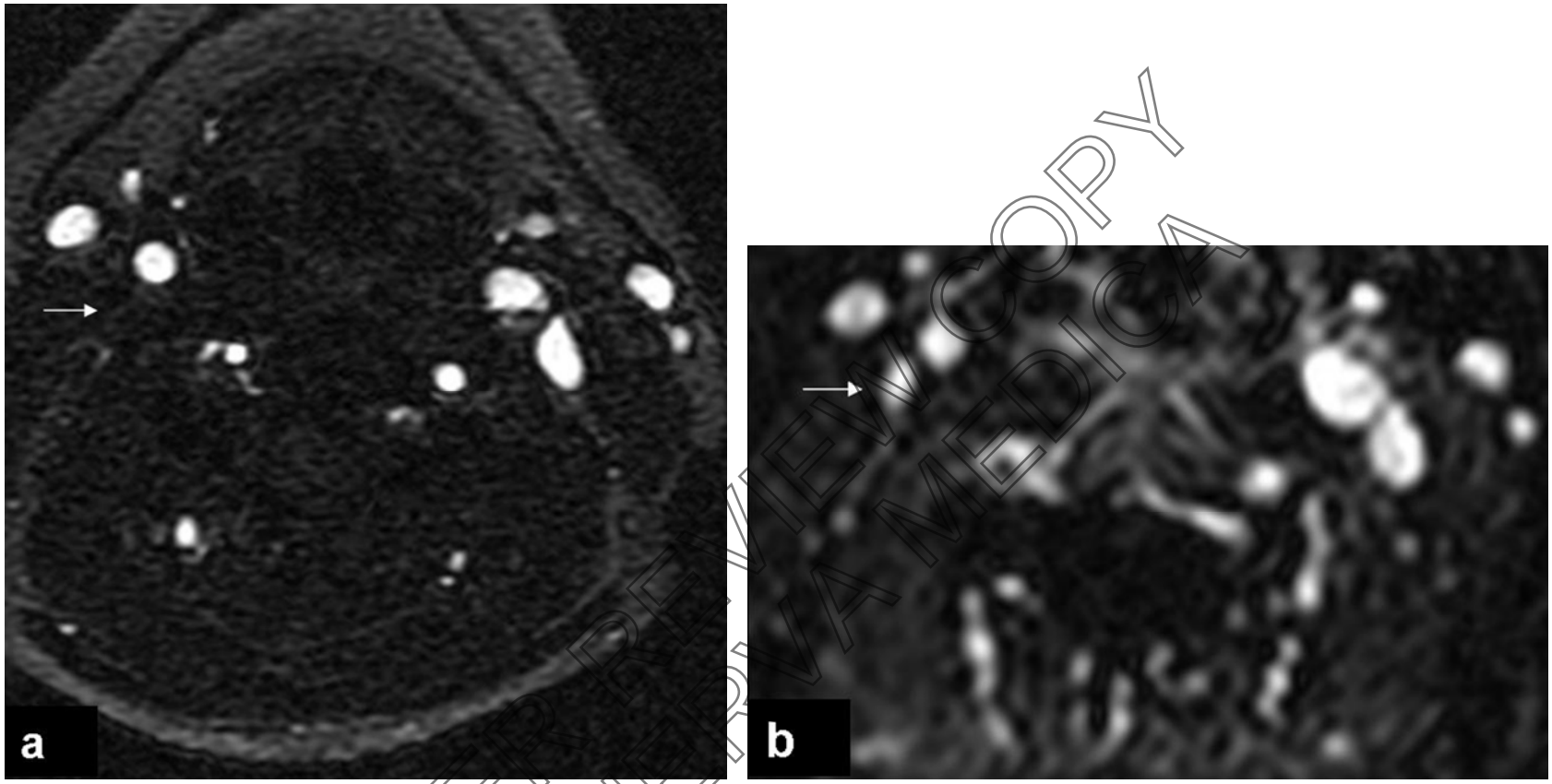


Figure 1

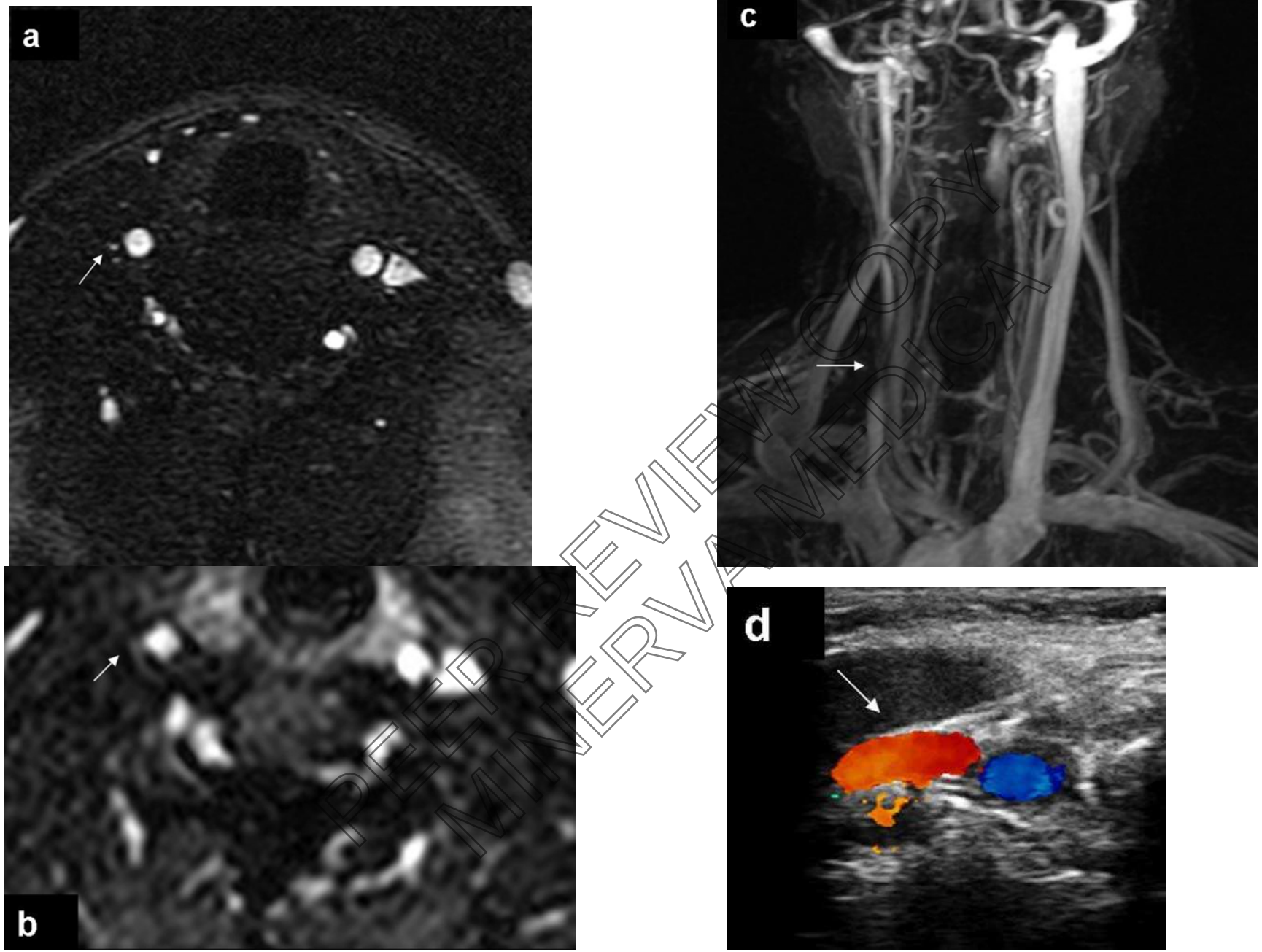
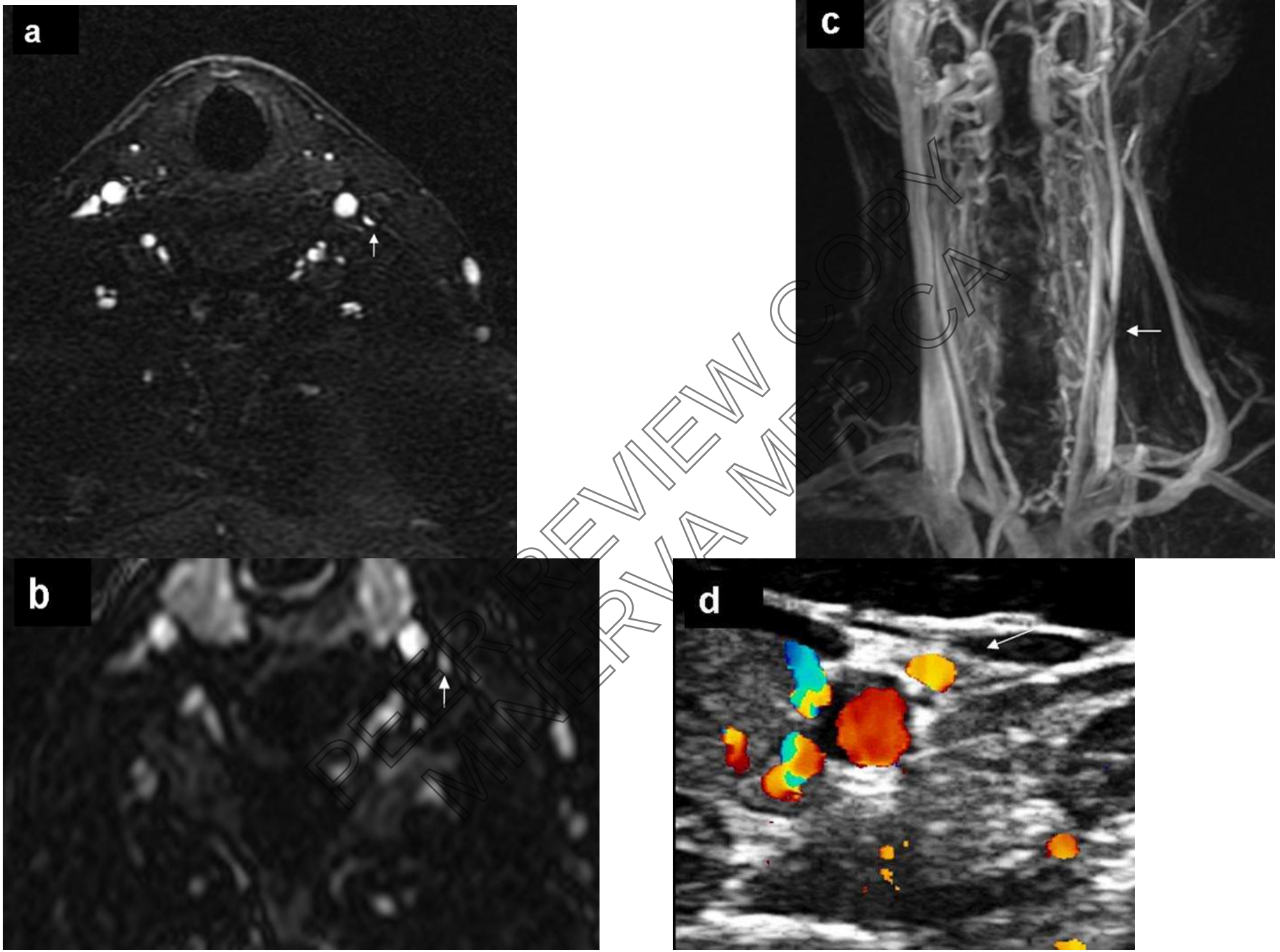


Figure 2

Figure 3



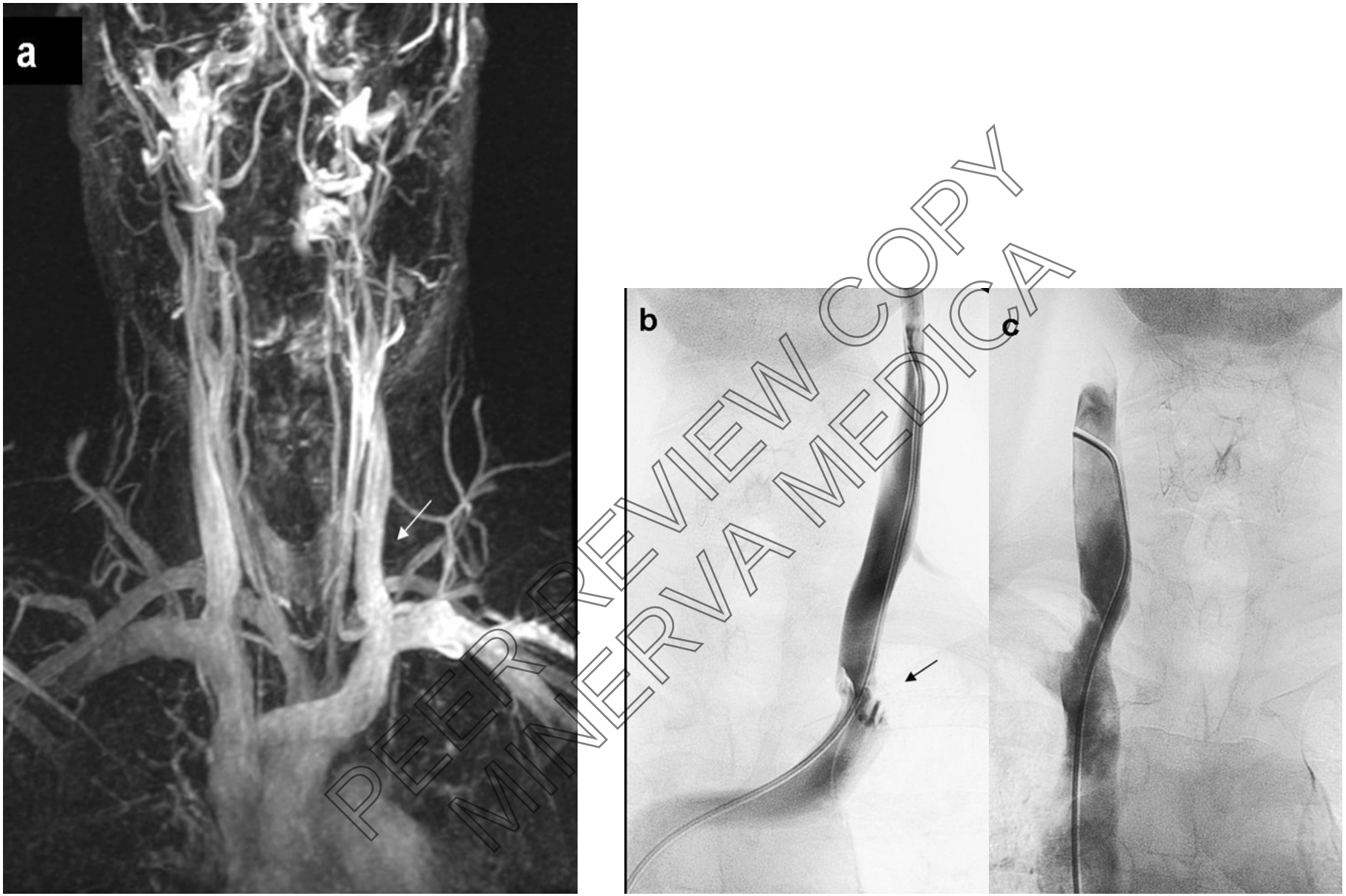


Figure 4

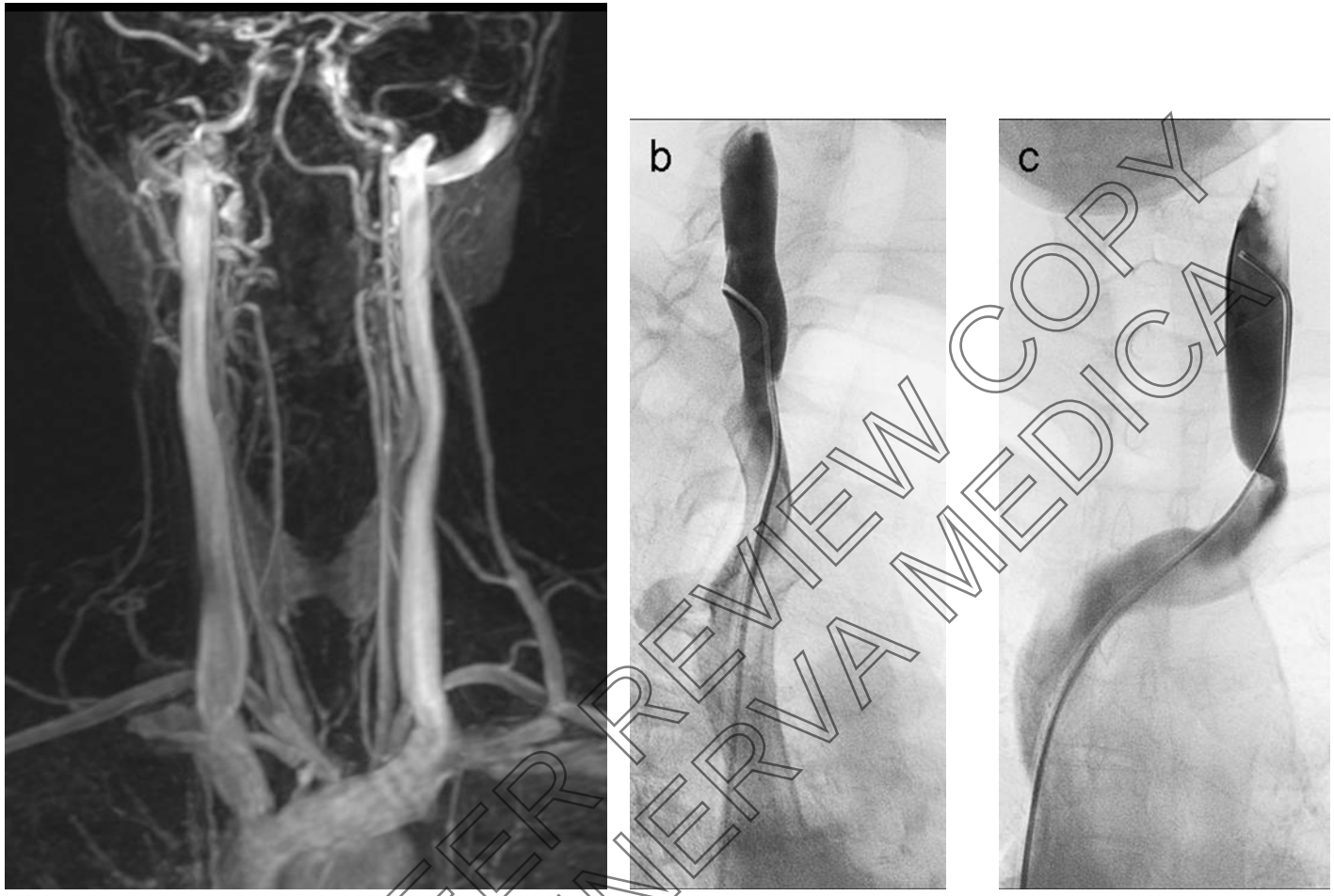


Figure 5

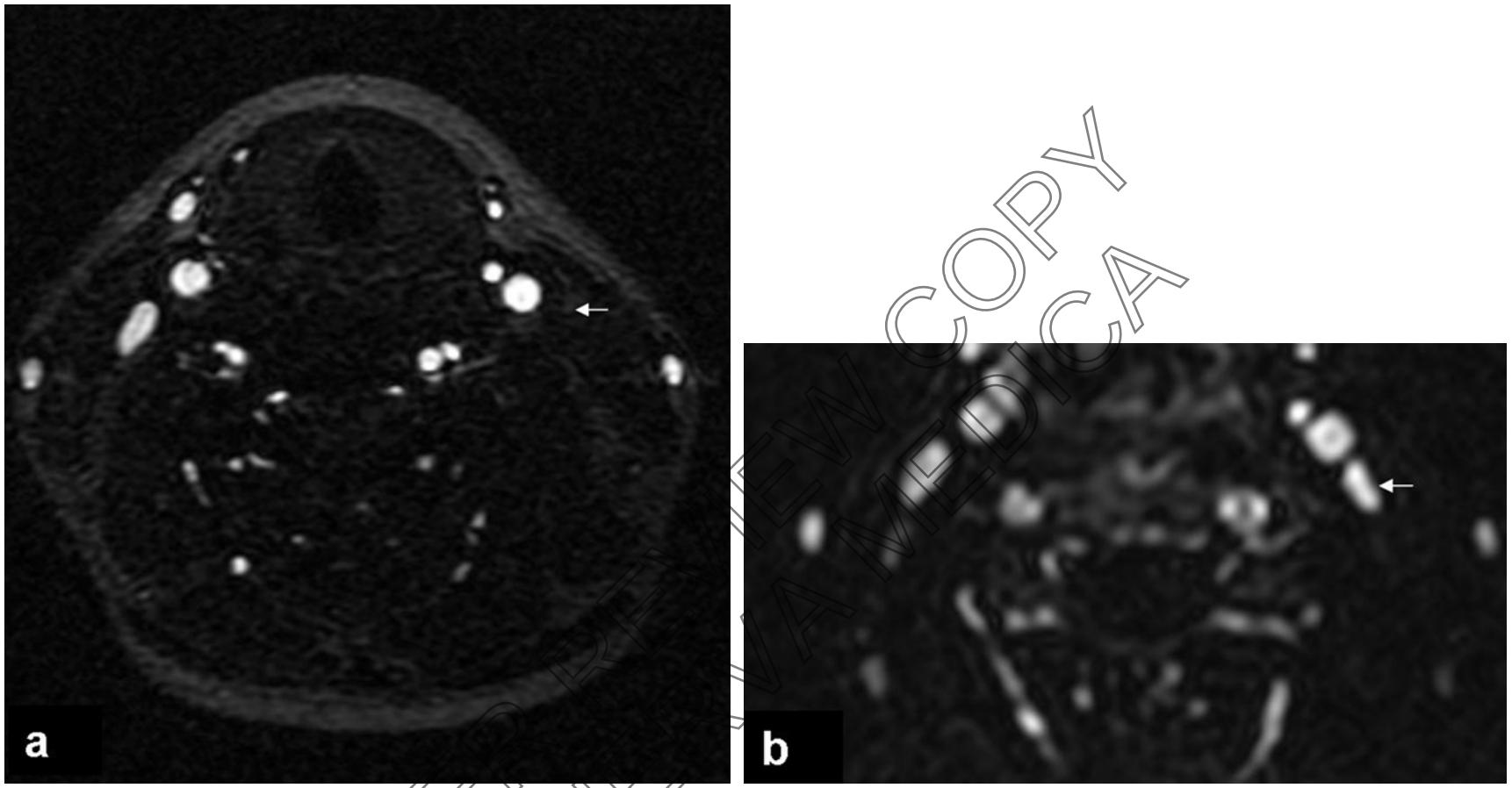


Figure 6

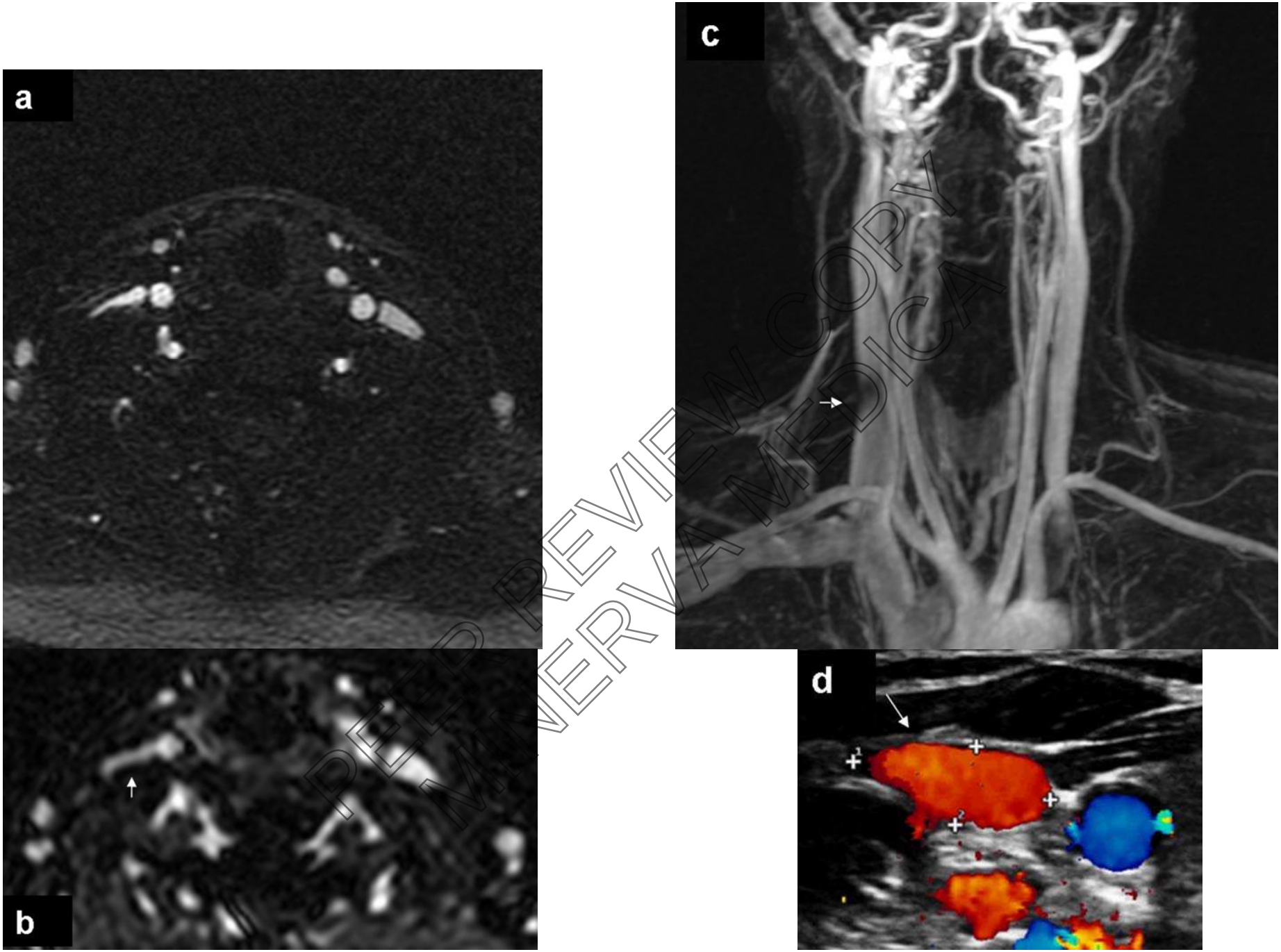
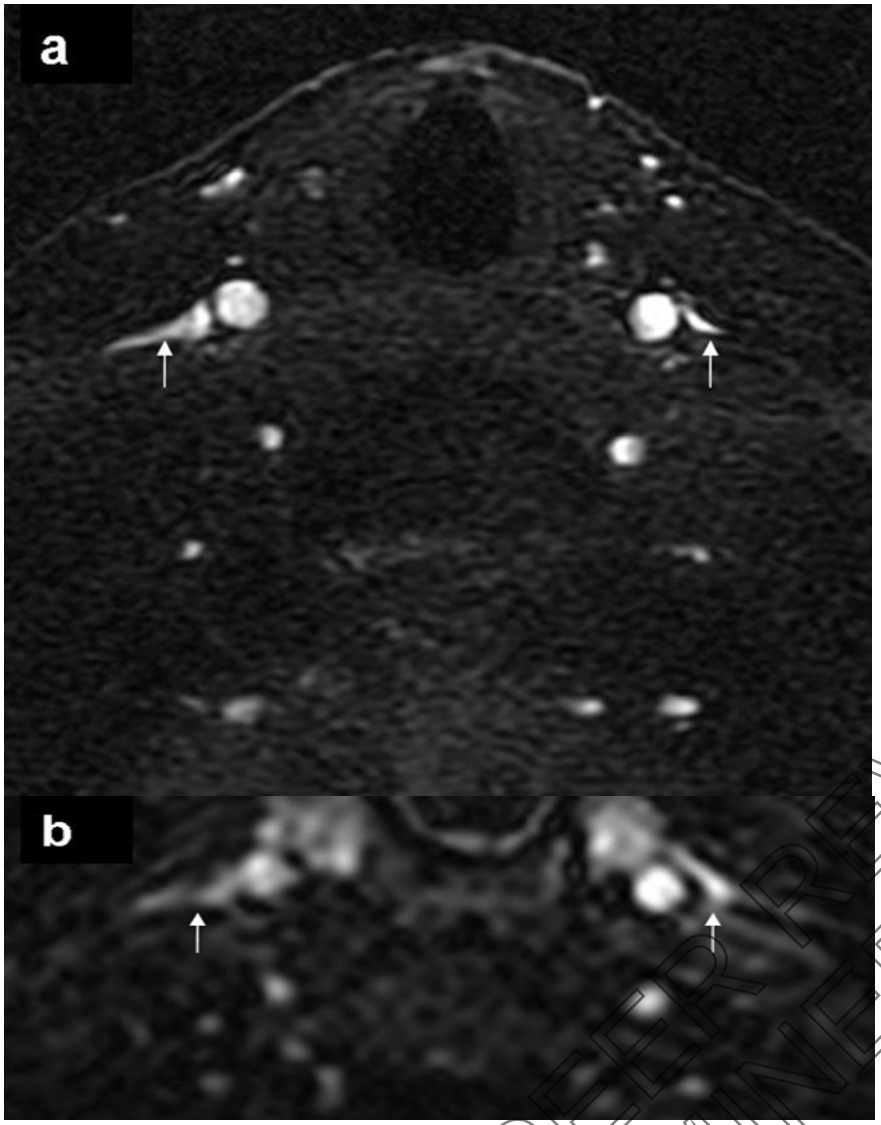
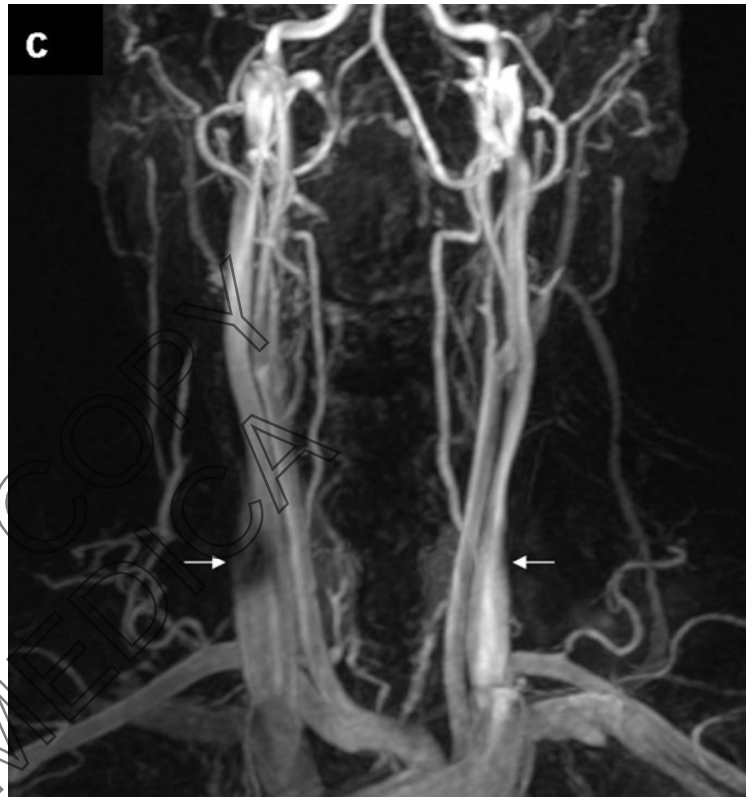
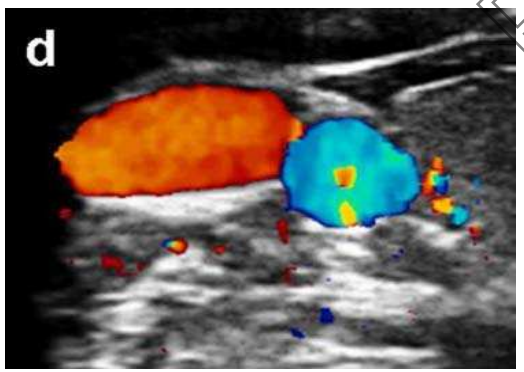


Figure 7







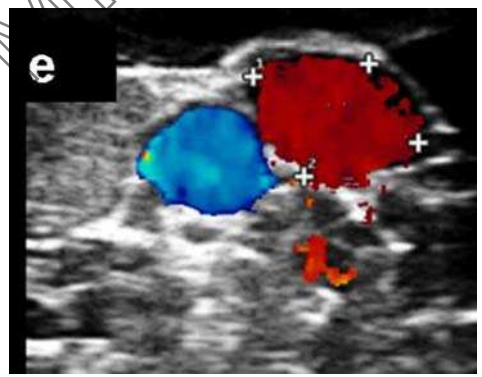


Figure 8