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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Aim. **Chronie cerebrospinal venDus 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 he non-invasively diagnosed by Doppler sonography** (DS) and invasively hy selective venography (SV). The **aim of this paper was to investigate the value of neck magnetie 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 He underwent OS, 20-**TIme.Of.Flight venography (TOF) and 3D·TIme Resolved Imaging of Contrast Kinetics angiography (TRICKS). MS patients also nnderwent SV. The internaljugnlarveins (UVs) **and the vertebral veins (VVs) were assessed by bath 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 He presented CCSVI, according to the DS criteria. This was confirmed by SV. For CCSVI diagnosis, DS showed sensitivity, specificitYI 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 shonld he inter**preted with caution and confirmed by other imaging techniques such as DS and SV.**

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Key words: Multiple sclerosis - Magnetic resonance imaging - Ultrasonography • Venography.

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Chronic cerebrospinal venous insufficiency (CCSVI) is a vascular condition characterized by anomalies in primary veins outside the skuIJ 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 internaljugularveins (INs) 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 colJaterals, very high incidence of reflux in both intracraniaI and extracranial venous segments, and loss of the postural regulation of cerebral venous outflow.[1,2] Type A pattern is characterized by stenoobstruction of the proximal AZY associated with a closed stenosis of one of the two INs, where a reflux is always present in the stenosed IN; type B pattern is characterized by bilateral stenoses of both INs and the proximal AZY where a reflux is present in all three venous segments; type C pattern is characterized by bilateral stenoses of both INs with a normal AZY system, where a reflux is present in the INs but not in the vertebral veins (Ws); type D pattern is characterized by muIti-level involvement of the AZY and lumbar system where a reflux is present in the Ws.

TABLE *L-Doppler sonography and selective venography findings in multiple sc/erosis patients and healthy controls.*

	Doppler pattern	Selective venography	CCsVI selective venography pattern	Wright finding	INleft finding	AZY finding	Lumbar vein finding
MSI	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
MSS	Abnormal	Abnormal	A	Annulus	Normal	**Membrane**	Normal
MS6	Abnormal	Abnormal	B	Annulus	**Septum**	**Membrane**	**Normal**
MS7	Abnormal	Abnormal	D	Normal	Annulus	Normal	**Dilatation**
MSS	Abnormal	Abnormal	C	Annulus	Malformed valve	Normal	Normal
MS9	Abnormal	Abnormal	B	Septum	Annulus	**Membrane**	Normal
MSID	Abnormal	Abnormal	B	Septum	Annulus	**Membrane**	Normal
HCI	Normal	Not performed	Not performed	Not performed	Not performed	Not performed	Not performed
HCZ	Normal	**Not perfonned**	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 perforrned**	Not performed	Not performed	Not performed	Not performed
HCS	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

MS: multiple sclerosis; He: healthy control; UV: internai 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 INs, where a reflux is always present in the stenosed UV; type B pattern is characterized by bilateral stenoses of bath INs and the proximal AZY, where a reflux is present in all three venous segments; type C pattern is characterized by bilateral stenoses of both DVs with a normal AZY system, where a reflux is present in the DVs but not in the vertebral veins (Ws); type D pattern is characterized by multilevel involvement of the AZY and lumbar system, where a reflux is present in the Ws.

Combined transcranial and extracranial echo-color-DS allows for non-invasive measurement of venous hemodynamic (VH) parameters indicative of CCSVI.l These VH parameters evaluate the presence of reflux in the IJVs anclJor in the VVs in sitting and in supine positions, presence of reflux in the deep cerebral veins (DCVs), presence of B-mode anomaly anclJor UV stenosis, absence of the flow in IJVs anclJor Ws, and presence of 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. 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).

Materials **and** 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,s 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 CUITent FDA-approved disease-modifying treatments and having normal renal function (creatinine clearance of >58 mL/min). Exclusion criteria included an acute relapse anclJor 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

TABLE *Il.-Comparison between Doppler sonography, magnetic resonance venography and selective venography findings of the internai jugular veins in patients with multiple selerosis and in healthy controls.*

	2D-TOF		3D-TRICKS		Doppler Sonography		Selective Venography	
	RIJV	LIJV	RIJV	LIJV	RIJV	LIJV·	RIJV	LIJV
MSI	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
MSS	Normal	Normal	Normal	Normal	Abnormal	Normal	Abnormal	Normal
MS6	Normal	Normal	Normal	Normal	Abnormal	Abnormal	Abnormal	Abnormal
MS7	Nortnal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
MSS	Abnormal	Abnormal	Abnormal	Normal	Abnormal	Abnormal	Abnormal	Abnormal
MS9	Normal	Abnormal	Normal	Normal	Abnormal	Abnormal	Abnormal	Abnormal
MSIO	Normal	**Normal**	Normal	Normal	**Abnormal**	Abnormal	Abnormal	Abnormal
HCI	Normal	Normal	**Normal**	Normal	Normal	Normal	Notperf.	Notperf.
HC2	Normal	Normal	**Normal**	Normal	Normal	Normal	Not perf.	Not perf.
HC3	Normal	Normal	Normal	**Normal**	Normal	Normal	Notperf.	Notperf.
HC4	Normal	Normal	Normal	Normal	**Normal**	Abnormal	Notperf.	Notperf.
HCS	Abnormal	Normal	Abnormal	Normal	Normal	Abnormal	Notperf.	Notperf.
HC6	Normal	Normal	Normal	Normal	Normal	Abnormal	Notperf.	Not perf.
HC7	Normal	Normal	Normal	Normal	Normal	Abnormal	Notperf.	Notperf.

MS: multiple sclerosis; He: healthy control; RUY: right internaI jugular vein; LIJV: left internaI jugular vein; 2D-TOF: 2D-Time-of-Flight venography; 3D-TRICKS: 3D· time resolved imaging of contrast kinetics venography; not perf.: not perfonned

renal function. The study was approved by the local Institutional Review Cominittee.

Magnetic resonance venography

All subjects were examined on a 3T GE Signa Excite RD 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 50 mT/m (zoom mode). A multi-channel head and neck (RDNV) coil manufactured by GE was used to acquire the following sequences: an enhanced and unenhanced 2D-Time-of-Flight (TüF) and 3D-Time Resolved Imaging of Contrast Kinetics (TRICKS) MRVs. The parameters used for 2D-TüF were: *TRITE* 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: *TRITE* 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 *2mJJs* using a pressure injector followed by a 20 mL saline flush. The total volume of contrast was 20m!, being the amount of the total volume (contrast plus saline solution) 40 mL. After acquisition of a 12 second mask (precontrast phase), the scanning of subsequent phases began simultaneously with the intravenous injection. The scan protocol consisted of 18 phases of acquisition, each of 5 second duration.

The flow morphology of the **IN**s was assessed on axial source images in unenhanced and enhanced 2D-TüF 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 **IN** can vary along the vesse!, we considered the narrowest point in both the inferior and the superior segments, respectively. Absent and pinpoint **IN** 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 extemal jugular veins *(ENs),* 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 than 5 mm in general, or higher than 7 mm in the inferior segment of the *EN* sinus that is often dilated.

All MRI scans were examined by two independent neuroradiologists (RD and ALS) in a blinded manner.

TABLE *III.-Sensitivity, specificity, accuracy, positive predictive and negative predictive value for Doppler sonography and magnetic resonance venography in relation to CCSVI diagnosis for detection of internaI jugular vein abnonnalities 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)

DS: Doppler sonography; 2D-TüF: 2D-TIme-of-Flight venography; 3D-TRICKS: 3D-lïme resolved imaging of contrast kinetics venography; PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval.

TABLE *N--Sensitivity, specificity, accuracy, positive predictive and negativejredictive value ofDoppler sonography and magnetic resonance venography in relation to selective venography (gol standard) for detection of internaI jugular* ***vein abnonnalities.***

	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)

DS: Doppler sonography; 2D-TDF: 2D-TIme-of-Flight venography; 3D-TRICKS: 3D· Time resolved imagîng of contrast kinetîcs venography; PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval.

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

The **IJV** MRV variable used for comparison with DS and SV was abnormal/norrnal flow, whereas the W variable used for comparison with DS (Ws 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 specifie predefined DS and SV assessment protocol, which was not part of this study.

Echo-c%r Dopp/er-sonography

Cerebr;al 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. AlI subjects were scannedfollowing the established protocol for diagnosis of CCSVI,l consisting of transcranial and extracranial echo-DS to measure the 5 VH parameters indicativè of CCSVI:

1. reflux in the IJVs and/or in the Ws 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 (internaI 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 less than or equal to 0.3 cm^2· Flaps, webs, septums, etc., in the lumen of IJVs were considered B-mode abnorrnalities;

4. flow that is not Doppler-detectable in IJVs and/or Ws 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 (EM) in a blinded manner. Presence of at least one of the following **IJV** 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 Ws was considered abnormal. DS abnorrnallnormal IJVs and Ws parameters were used for comparison with MRV and SV.

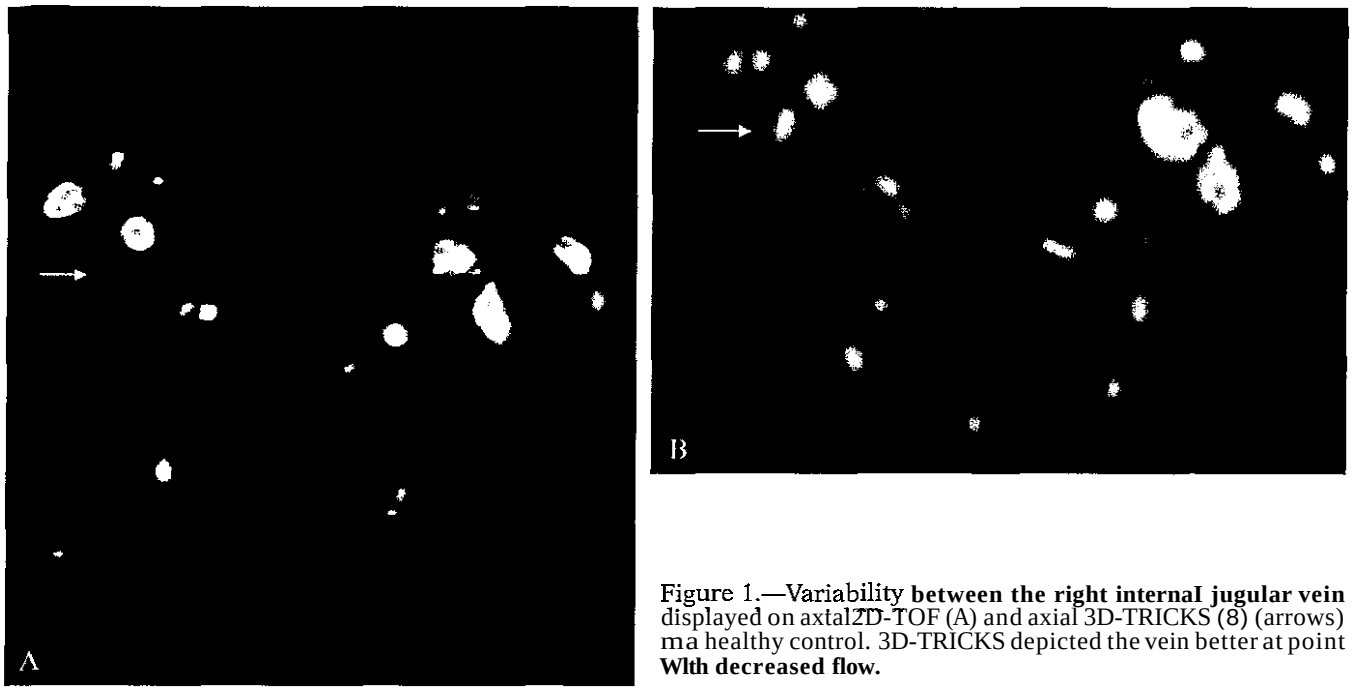

Figure 1.—Variability between the right internal jugular vein displayed on axial 2D-TOF (A) and axial 3D-TRICKS (B) (arrows) in a healthy control. 3D-TRICKS depicted the vein better at point with decreased flow.

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 INs.[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 (RG). Presence of at least one of these anomalies in INs and VVs 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-TüF 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 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 INs as a gold standard, we calculated the sensitivity, specificity, accuracy, PPV and NPV for 3D-TRICKS, 2D-TüF and the DS for left and right INs. The true-positive was defined as an abnormal imaging finding on 3D-TRICKS, 2D-TüF or DS and presence of abnormal IN 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 abnor-

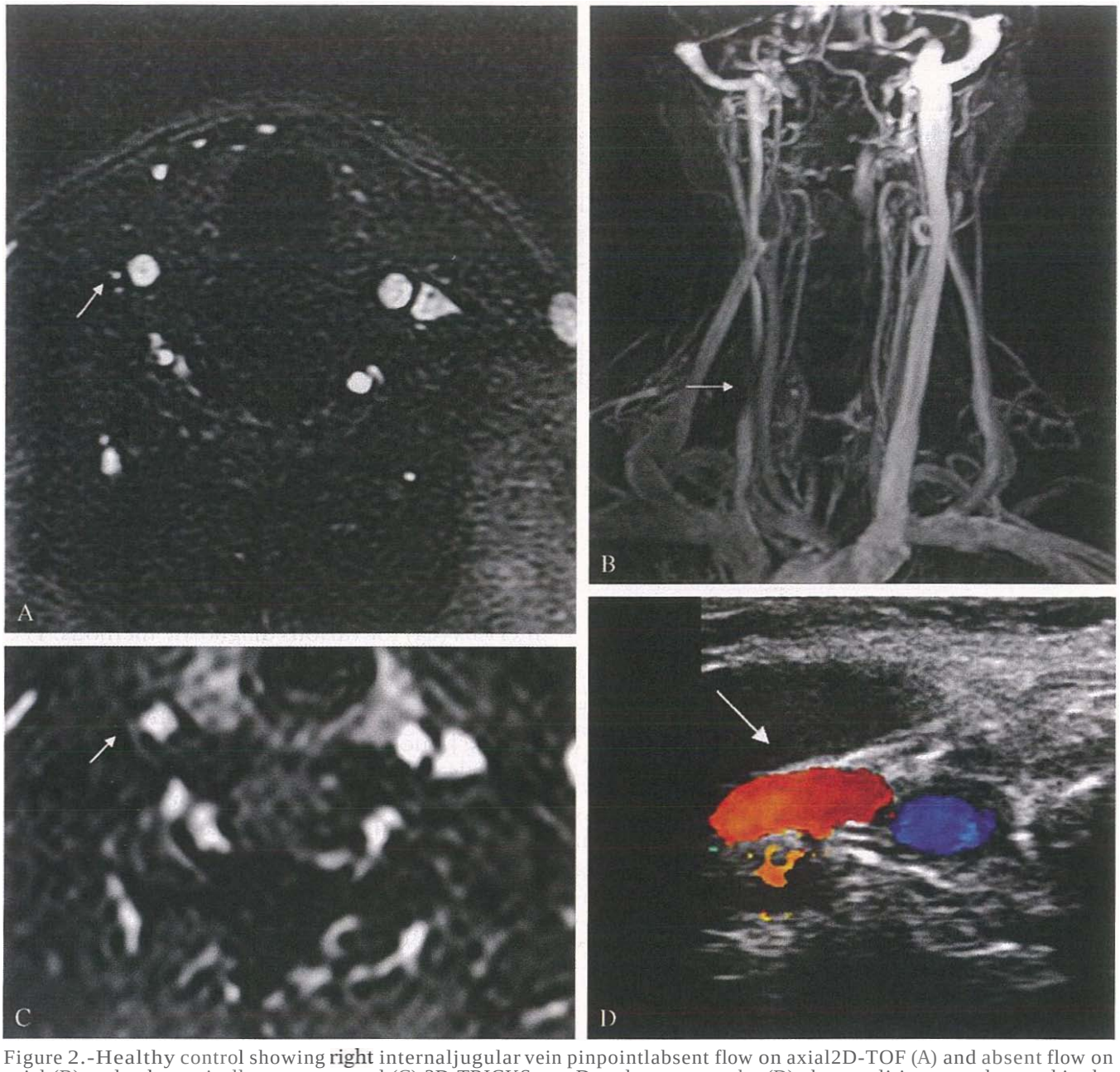

Figure 2.-Healthy control showing **right** internaljugular vein pinpointlabsent flow on axial2D-TOF (A) and absent flow on axial (B) and volumetrically reconstructed (C) 3D-TRICKS. 0 Doppler sonography (D) abnonnalities were detected in the **right internal jugular vern.**

mality on SV, and true-negative as a normal imaging finding in the absence of abnormality on SV.

Results

Demographie and clinieal eharaeteristies

The mean age of the MS patients was 36.4 years (Sn 7.3), mean disease duration 8.4 years (sn 1.8) and median EnSS 2.5. Seventy percent of the MS patients were females. The proportion of females to males (P=O.69, Fisher Exact test) and the mean age of the two groups (P=O.sS9) were similar. AlI MS patients were on disease-modifying therapy (three were on subcutaneous interferon-beta la, two on intramuscular interferon-beta la, three were on natalizumab and two were on glatiramer acetate).

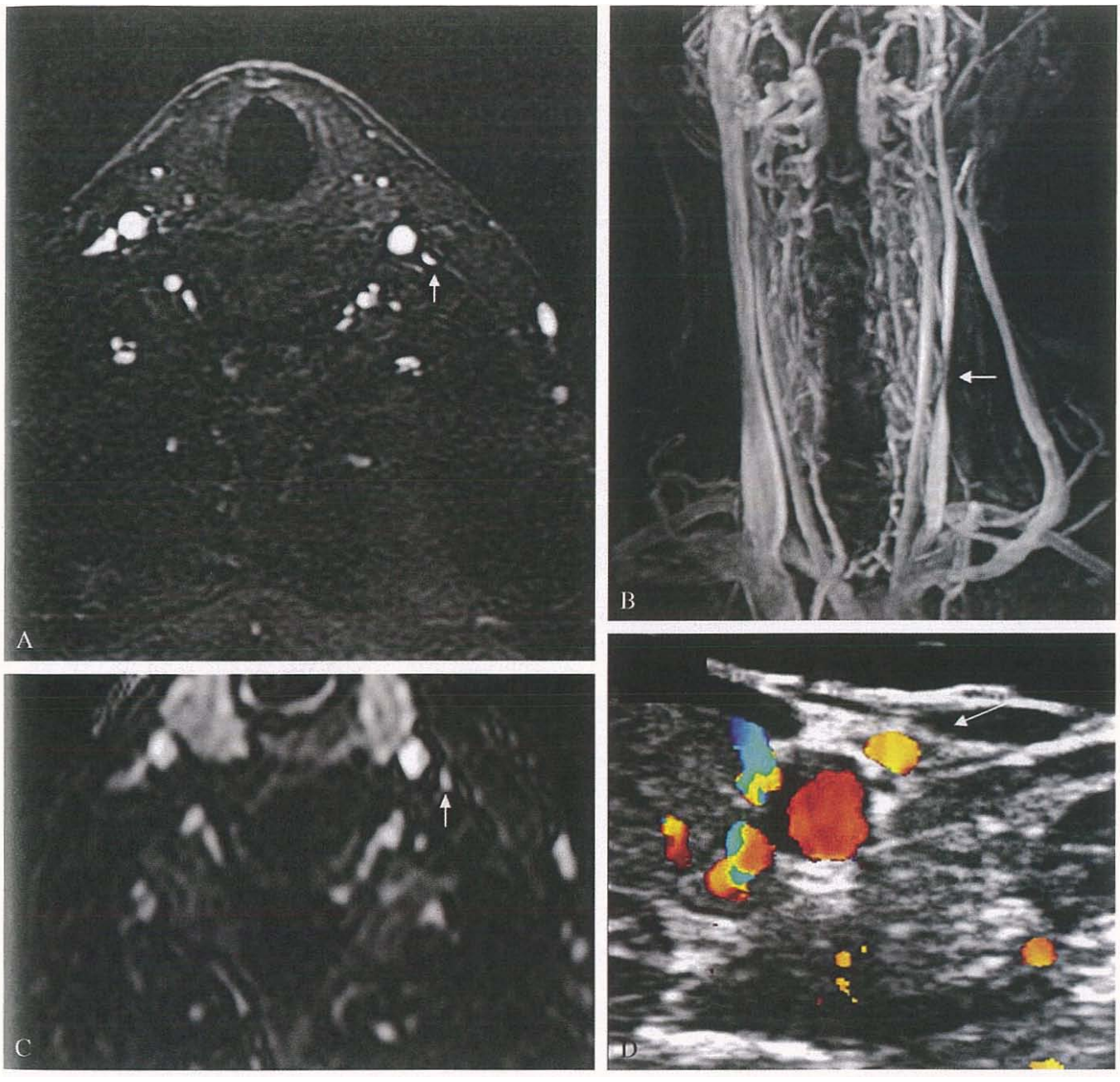

Figure 3.-Good overlap between narrowing of left internaI jugular veins on axial 2D-TOF (A), axial (B) and volumetrically reconstructed (C) 3D-TRICKS and Doppler sonography (D) in multiple sclerosis patient. All three techniques showed similar findings in left internaI jugular vein.

Comparison between multiple sclerosis patients and healthy contrais

Table l shows DS results in MS patients and He, and the SV findings in MS patients. All MS patients and none of the He presented cesV! 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 He (P<O.OOl). DS, MRV and SVabnormality findings for the left and right IJVs in MS patients and HC are shown in Table II. For CCSV! 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-TüF in the IJVs (Table III).

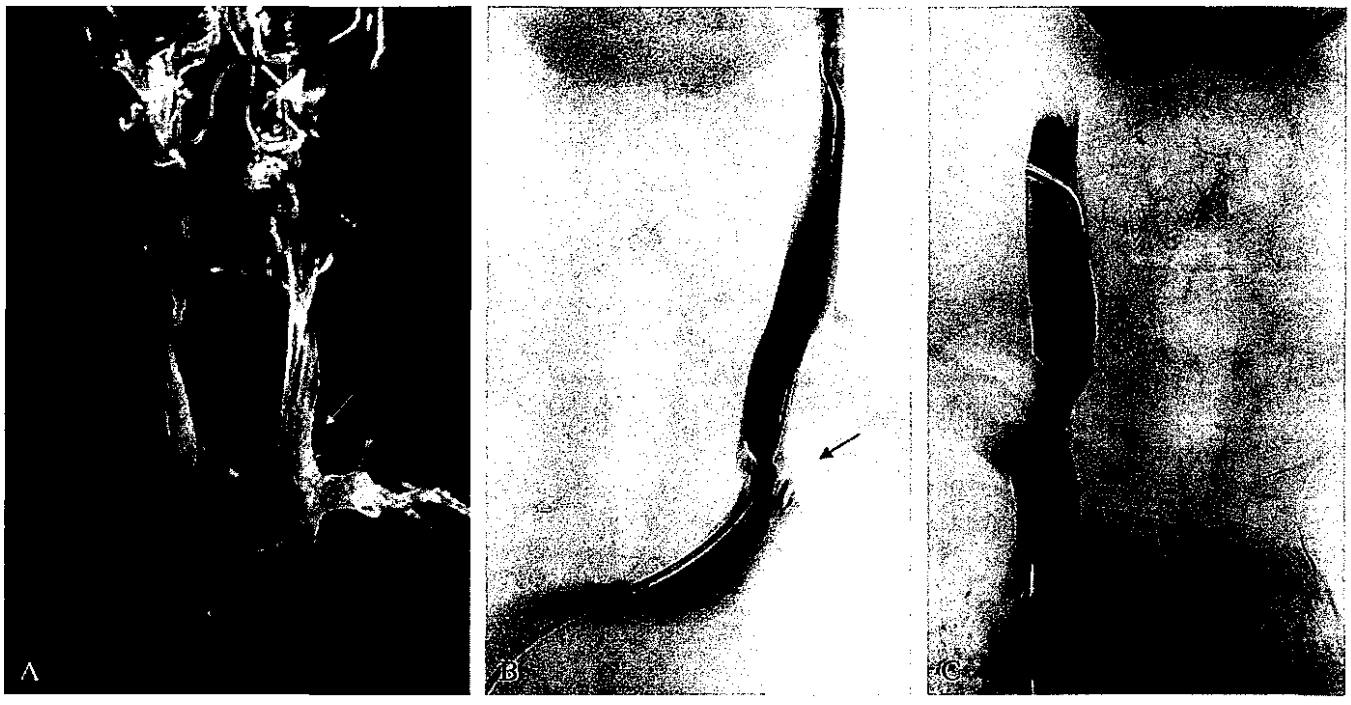

Figure 4.-3D-TRICKS (A) shows nonnalleft internai jugular vein, whereas selective venography (B) shows stenosis in patient **with multiple sc1erosis. Selective venography shows 'normal right internaI jugular vein (C).**

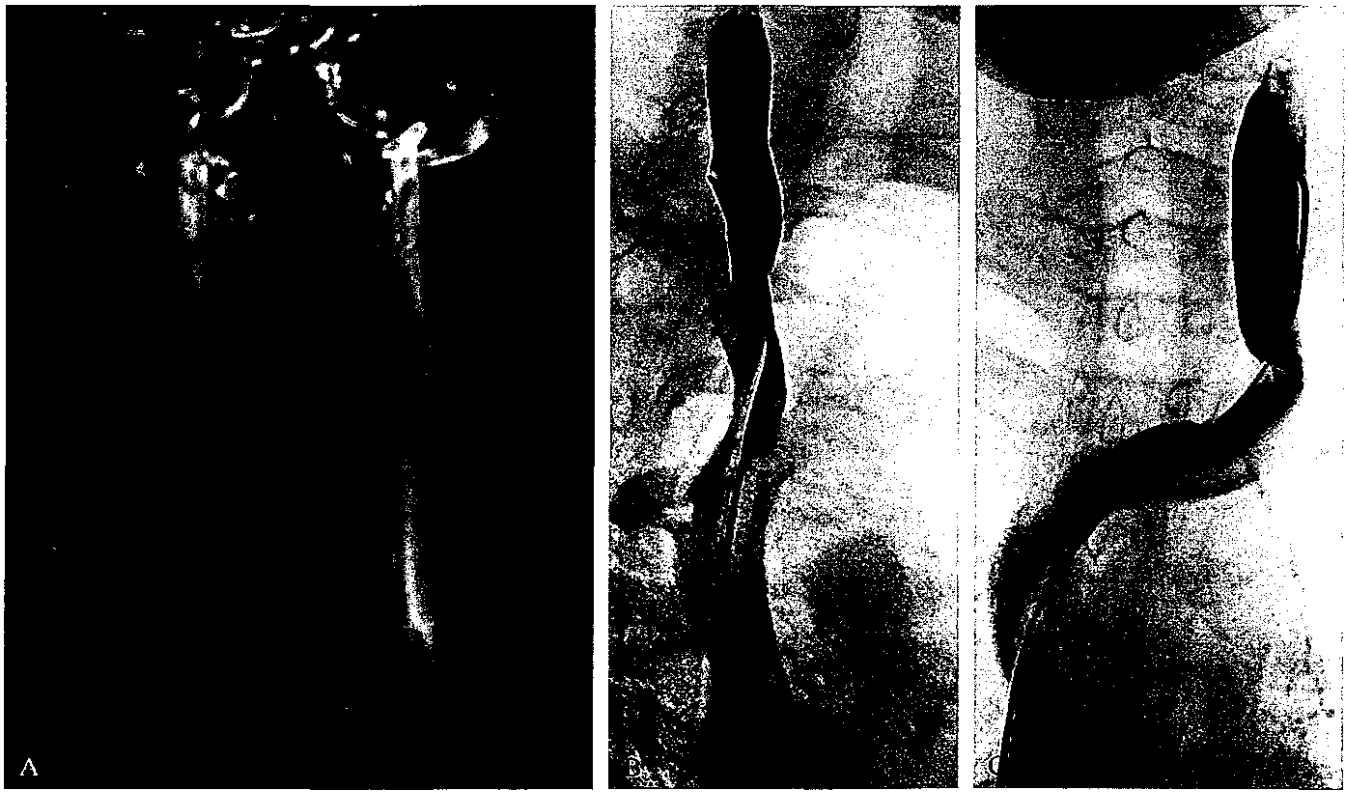

Figure 5.—3D-TRICKS (A) shows normal internaI jugular **veins in MS patient, whereas selective venography shows bilateraI internaI jugular vein abnonnalities characterlzed by a septum in the right internaI jugular vein (B) and an annulus in the** left internai jugular vein (C). Doppler sonography confinned selective venography findings.

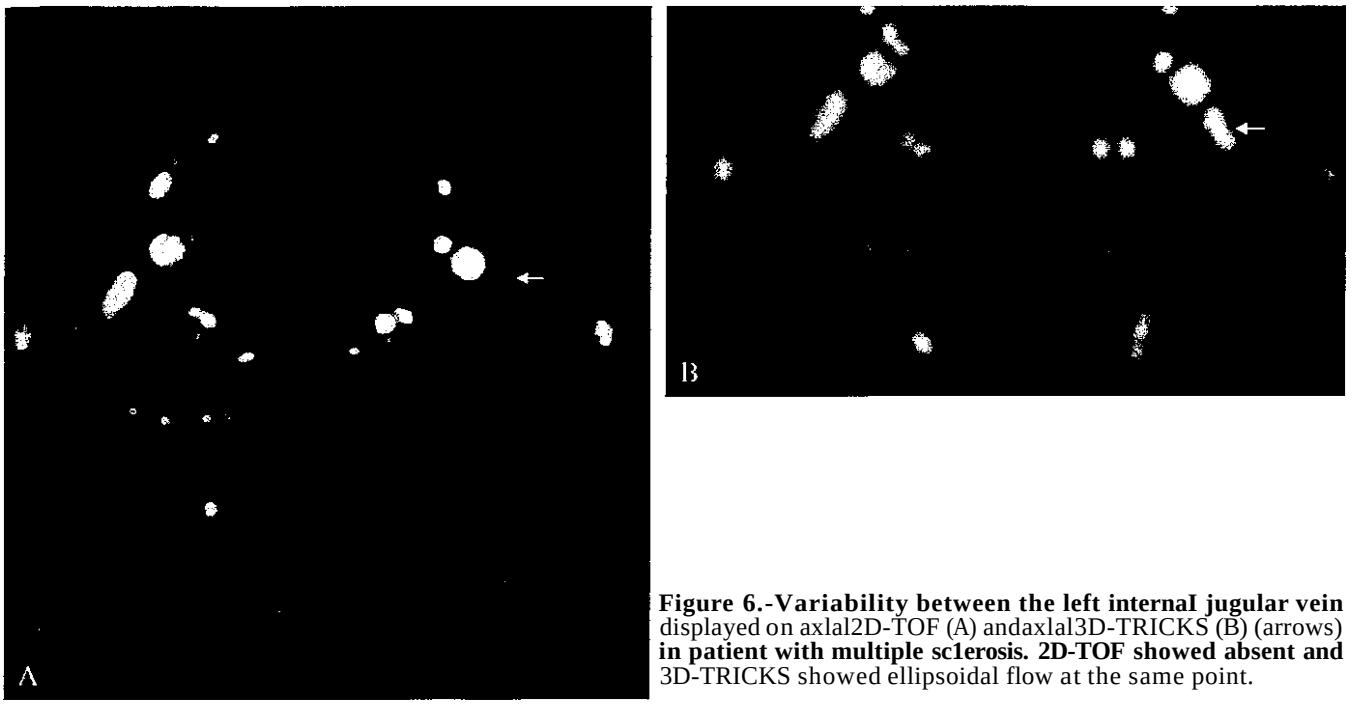

Figure 6.-Variability between the left internaI jugular vein displayed on axlal2D-TOF (A) andaxlal3D-TRICKS (B) (arrows) **in patient with multiple sc1erosis. 2D-TOF showed absent and** 3D-TRICKS showed ellipsoidal flow at the same point.

TABLE *v'-Variability of the morphology of the internai jugular veins in healthy controls and multiple sc/erosis patients for 3D-TRICKS versus 2D-TOF in relation ta flattening.*

	2D-TDF				3D-TRICKS			
	sRIJV	sUN	iRIJV	iLUV	sRIJV	sLUV	iRIJV	iLUV
MS!	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
MSS	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
MSS	NoF	NoF	NoF	NoF	F	NoF	NoF	NoF
MS9	NoF	NoF	F	NoF	NoF	NoF	F	F
MS!ü	NoF	NoF	F	NoF	NoF	NoF	F	NoF
HC!	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
HCS	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

MS: multiple sclerosis; He: healthy control; s: superior segment; i: inferior segment; RIlV: right internai jugular vein; LIJV: left internaI jugular vein; F: flattened; NoF: non flattened.

Comparison between MRV, 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 IV). The DS figures were 100%, 75%, 95%, 94% and 100%, respectively. We detected flow in ail VVs explored by MRV. There were 2 MS patients who showed blockage of the VVs in DS without

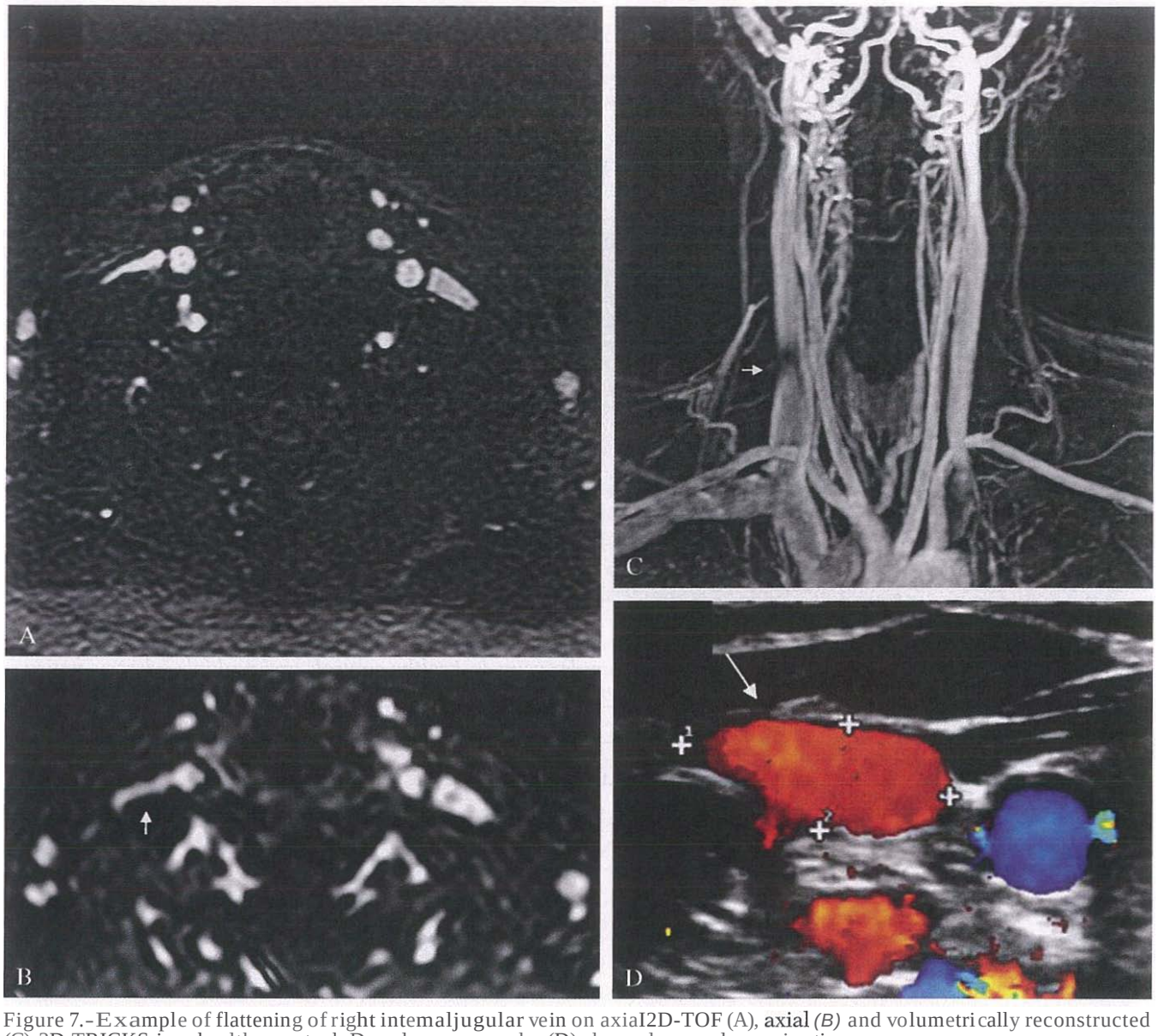

Figure 7.-Example of flattening of right internal jugular vein on axial 2D-TOF (A), axial (B) and volumetrically reconstructed (C) 3D-TRICKS in a healthy control. Doppler sonography (D) showed normal examination.

correlation with MRY, where vertebral flow was visualized.

In 57.1% *(417)* of the HC there was no overlap between MRV and DS findings. In 42.8% *(317)* of the HC, MRV showed variability in the morphology of the IJVs between both sequences (Table II and Figures 1, 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 variabiHty 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 V 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-TüF. In MS patients, com-

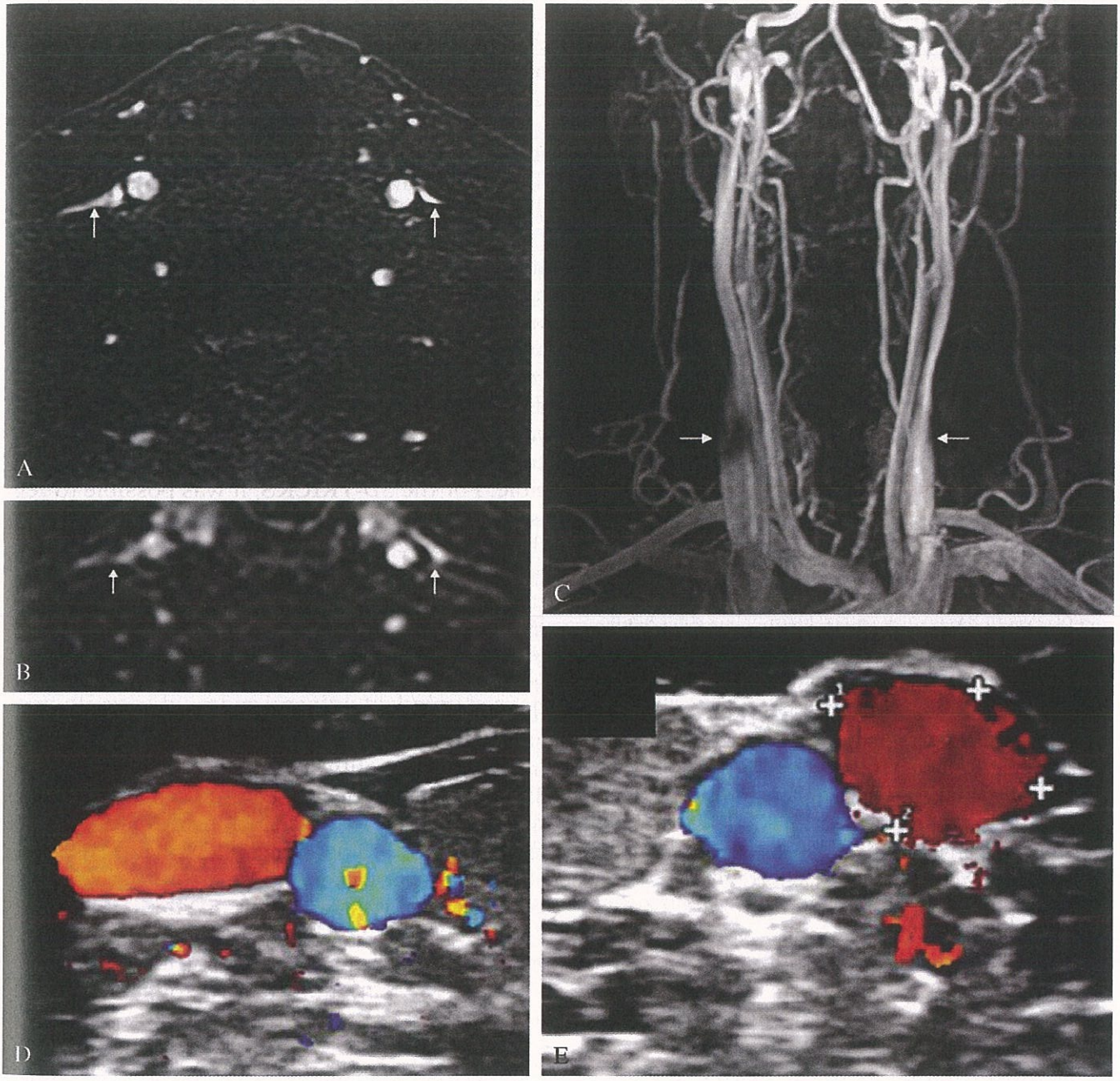

Figure 8.—Example of bilateral flattening of internal jugular veins on axial 2D-TOF (A), axial (B) and volumetrically reconstructed (C) 3D-TRICKS in a healthy control. Doppler sonography (D,E) showed normal examinations.

pared 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 described was 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 1,6). 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, 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, 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 V).

In relation to these technical flow-related limitations, others have 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: 1) a predominant jugular-drainage, which was present in 72% of all individuals; 2) a balanced jugular/extrajugular drainage present in 22% of the subjects; and 3) 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 II, Figures 2, 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 use-

ful 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.

Conclusions

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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