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ORIGINAL
RESEARCH

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BACKGROUND AND PURPOSE: Chronic cerebrospinal venous insufficiency (CCSVI) is a vascular condition characterized by anomalies of the main extracranial cerebrospinal venous routes that interfere with normal venous outflow. Research into CCSVI will determine its sensitivity and specificity for a diagnosis of MS, its prevalence in MS patients, and its clinical, MRI, and genetic correlates. Our aim was to investigate the prevalence and number of intra- and extraluminal structural and functional extracranial venous abnormalities by using DS and MRV, in patients with MS and HCs.

MATERIALS AND METHODS: One hundred fifty patients with MS, 104 (69.3%) with RR and 46 (30.7%) with a progressive MS course, and 63 age- and sex-matched HCs were scanned with 3T MR imaging by using TOF and TRICKS sequences (only patients with MS). All subjects underwent DS examination for intra- and extraluminal structural and functional abnormalities of the IJVs. Absent/pinpoint IJV flow morphology on MRV was considered an abnormal finding. Prominence of collateral extracranial veins was assessed with MRV.

RESULTS: Patients with MS had a significantly higher number of functional ($P < .0001$), total ($P = .001$), and intraluminal ($P = .005$) structural IJV DS abnormalities than HCs. There was a trend for more patients with MS with extraluminal IJV DS abnormalities ($P = .023$). No significant differences were found on the MRV IJV flow morphology scale between patients with MS and HCs. Patients with progressive MS showed more extraluminal IJV DS abnormalities ($P = .01$) and more MRV flow abnormalities on TOF ($P = .006$) and TRICKS ($P = .01$) than patients with nonprogressive MS. There was a trend for a higher number of collateral veins in patients with MS than in HCs ($P = .016$).

CONCLUSIONS: DS is more sensitive than MRV in detecting intraluminal structural and functional venous abnormalities in patients with MS compared with HCs, whereas MRV is more sensitive in showing collaterals.

ABBREVIATIONS: CCSVI = chronic cerebrospinal venous insufficiency; CV = catheter venography; DS = Doppler sonography; EDSS = Expanded Disability Status Scale; Gd = gadolinium; HC = healthy control; ICC = interclass correlation coefficient; IJV = internal jugular vein; MRV = MR venography; PP = primary-progressive; RR = relapsing-remitting; SP = secondary-progressive; TOF = time-of-flight; TRICKS = time-resolved imaging of contrast kinetics; VV = vertebral veins

MS is an autoimmune disease of the CNS that is a result of interaction between genetic, environmental, and infectious factors.¹⁻⁴ Recently, a condition called CCSVI was found with high frequency in patients with MS.⁵ CCSVI presupposes that MS is associated with impaired venous drainage from the brain to the periphery due to venous anomalies in major extracranial neck and azygos veins.⁵

Recent studies by using extra- and transcranial DS,⁶⁻¹⁰

phase-contrast and contrast-enhanced MRV,¹¹⁻¹³ or CV^{14,15} failed to confirm the high frequency of abnormal cerebral venous outflow in patients with MS versus HCs, as originally reported.⁵

Previous CV studies in MS^{5,14-16} proposed that the extracranial venous anomalies are likely to be truncular venous malformations characterized by intraluminal defects (such as flaps, webs, septa, membranes, and malformed valves) or by extraluminal abnormalities represented by stenoses of the venous wall.

Therefore, in this study, we aimed to define the frequency of those venous abnormalities in patients with MS and HCs by using 2 noninvasive imaging techniques (DS and MRV).

Materials and Methods

Subjects and Clinical Assessments

The case-control prospective study included 150 consecutive patients with MS and 63 age- and sex-matched HCs who participated in the combined transcranial and extracranial venous Doppler study and fulfilled inclusion and exclusion criteria.⁶ The study started in April 2009 and is still enrolling subjects. Inclusion criteria for patients with

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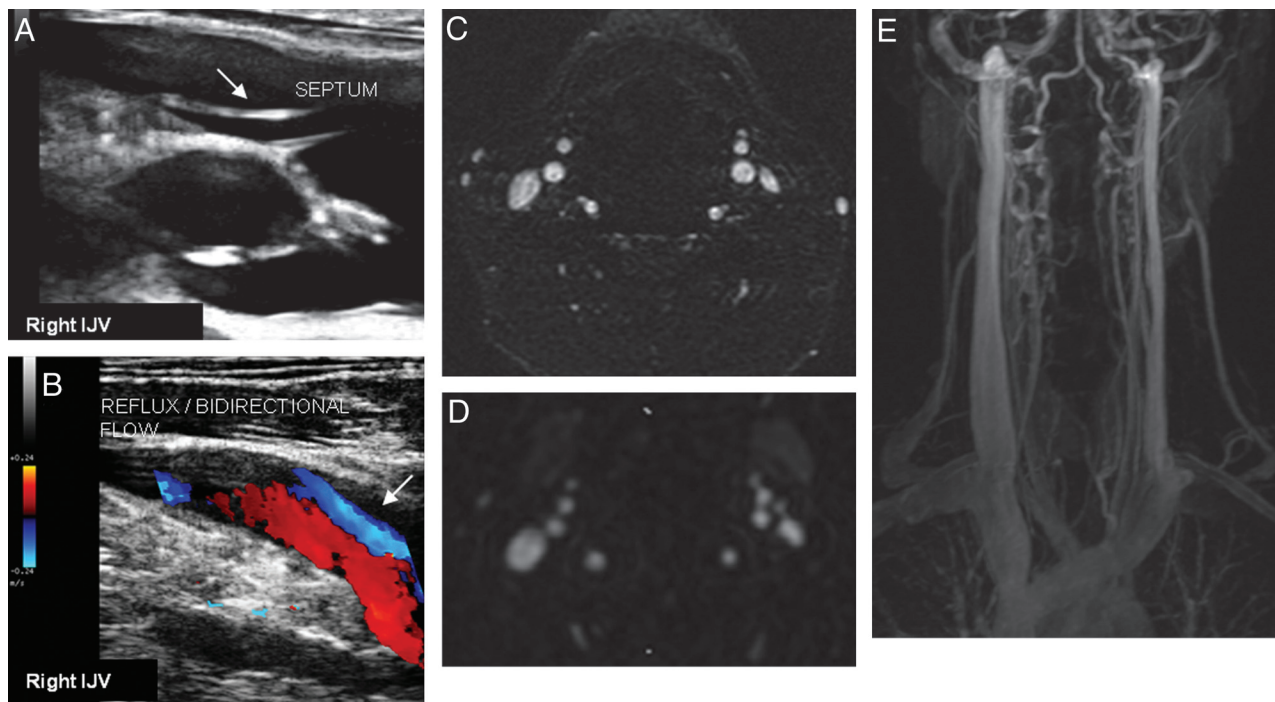


Fig 1. Intraluminal (septum, *A*) structural abnormality in the right IJV causing significant reflux/bidirectional flow directed toward the brain for a duration of >0.88 seconds in both the supine and sitting positions (*B*), as detected by using DS, in a 33-year-old woman with RRMS with 2 years of disease duration and minimal disability (EDSS score, 1.0). 2D TOF (*C*) and enhanced 3D TRICKS (*D* and *E*) sequences show normal flow morphology.

MS were clinically definite MS,¹⁷ RR-, SP-, and PPMS disease course¹⁸; 18–65 years of age; an EDSS score from 0 to 6.5¹⁹; and diagnostic evaluation for extracranial venous anomalies by using DS and MRV examinations. Exclusion criteria were occurrence of relapse and steroid treatment in the 30 days preceding study entry, pre-existing medical conditions known to be associated with neck pathology, history of cerebral congenital vascular malformations, pregnancy, contraindication for receiving Gd-based contrast agents in patients with MS, history of chronic obstructive pulmonary disease, and arthritic necks (may not be able to lie flat).⁶ The study was approved by the local institutional review board, and informed consent was obtained from all subjects.

DS

Participants underwent extracranial DS of the neck. A color-coded DS scanner (MyLab 25; Esaote-Biosound, Irvine, California) equipped with a 7.5- to 10-Mhz transducer was used to examine venous return in the IJVs and VVs. All subjects were examined first in the supine and then in the sitting position (0° and 90°). The DS examination was performed by 2 trained technologists who were blinded to subjects' characteristics, as previously described.⁶

The IJV abnormalities were divided into 3 subcategories (Figs 1–3): intraluminal structural (web, flap, septa, membrane, and malformed valve), extraluminal structural (stenosis and annulus), and functional abnormalities (presence of reflux/bidirectional flow, paradox, and no flow). The proposed classification and description of these abnormalities are given in Table 1.

Absence of detectable flow in VVs was considered abnormal and was compared with abnormal findings of VV on MRV.

To test the intra- and inter-rater reproducibility of the intra-, extraluminal, and functional venous abnormalities, 32 subjects (20 patients with MS, 7 HCs, and 5 controls with other neurologic dis-

eases) were examined by 2 Doppler technicians who assessed all subjects twice during a 1-week period in a blinded manner.⁶

All DS examinations were double-checked and confirmed by 2 independent neuroradiologists in a blinded manner (D.H. and K.D.).

MRV

All patients with MS and HCs underwent unenhanced 2D-TOF and enhanced 3D-TRICKS sequences (in patients with MS) on 3T MR imaging (Figs 1 and 3). The participation of the HCs in the contrast portion of the MRV protocol was not recommended by our institutional review board.

MRV Acquisition Protocol

All subjects were examined on a 3T Signa Excite HD 12.0 TwinSpeed 8-channel scanner (GE Healthcare, Milwaukee, Wisconsin), with a maximum slew rate of 150T/m/s and a maximum gradient amplitude in each orthogonal plane of 50 mT/m (zoom mode). A multichannel head and neck coil manufactured by GE Healthcare was used to acquire the following sequences: TOF and TRICKS MRV. The parameters used for TOF were the following: TR/TE, 17/4.3 ms; flip angle, 70°; 1.5-mm section thickness; acquisition matrix, 320/192; and acquisition in the axial scan plane. The parameters used for TRICKS were the following: TR/TE, 4.2/1.6 ms; flip angle, 30°; 2-mm section thickness; acquisition matrix, 320/192; and acquisition in the coronal scan plane. Intravenous Gd contrast was injected at a rate of 2 mL/s by using a pressure injector. The total volume of contrast was 20 mL. The scan protocol consisted of 18 phases of acquisition, each of 5 seconds' duration. The MR images were obtained from the level of the confluens sinuum to the level of the aortic arch.

The MRV analysis protocol has been previously described in detail.¹³ Briefly, the flow morphology of the IJVs was assessed on axial source TOF

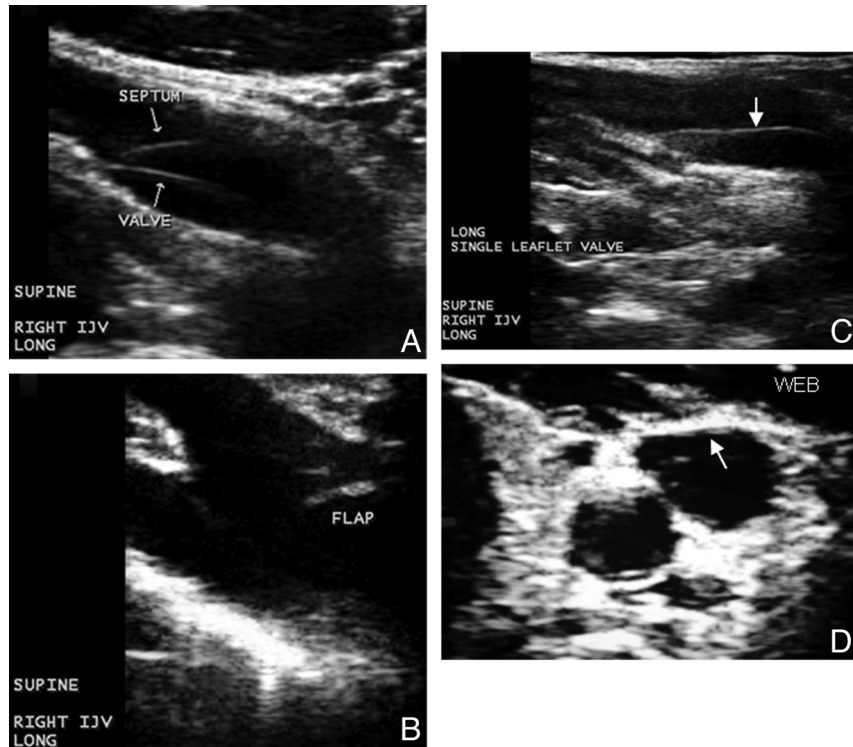


Fig 2. Examples of intraluminal structural abnormalities in the IJVs causing hemodynamic abnormality in HCs and patients with MS, 22 and 47 years of age. *A*, septum. *B*, Flap. *C*, Single leaflet valve. *D*, Web.

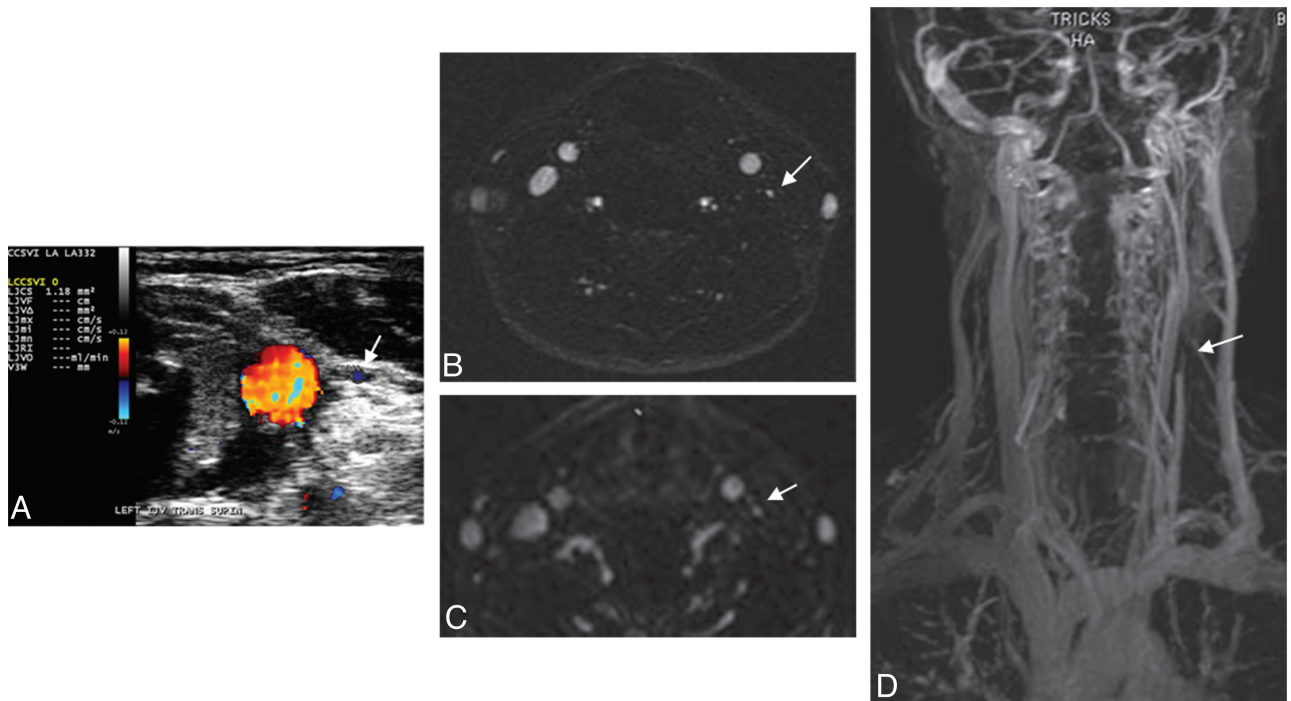


Fig 3. Extraluminal structural abnormality in the left IJV causing significantly reduced flow in both the supine and sitting positions, as detected by using DS (*A*) and MRV (*B–D*) in a 46-year-old woman with SPMS with 20 years of disease duration and advanced disability (EDSS score, 5.0). 2D TOF (*B*) and enhanced 3D TRICKS (*C* and *D*) sequences show pinpoint flow morphology.

images as well as on axial reconstructed TRICKS sections. The flow was evaluated on an ordinal scale ranging from absent (no visible flow) to ellipsoidal (patent lumen). We assigned 5 qualitative flow-morphology categories: absent, pinpoint, flattened, crescentic, and ellipsoidal.¹³ We considered only absent and pinpoint flow in the IJVs as abnormal. VV flow was classified as absent (abnormal)/present (normal).

We also assessed the left and right prominence of the other most important veins in the neck visible on MRV: external jugular veins, anterior jugular veins, facial veins, thyroid veins, and deep cervical veins, as previously reported.¹³ The prominence was graded as absent/present, and the number of collateral veins for the right and left side of the neck was also counted.

Table 1: Proposed classification of IJV abnormalities on DS

DS Classification	Types/Examples
Intraluminal structural venous abnormality; this is an echogenic structure extending from the endothelial lining of the vein wall with/without presence of functional abnormality; these abnormalities include web, flap, septum, membrane, and malformed valve	Web: multiple septa and/or flaps located in a cluster Flap: thin linear echogenic structure extending from endothelial lining of vein wall Septum: thin linear echogenic structure extending from endothelial lining of vein wall, and attached to it at both ends; septum may extend across a vein to attach on opposing sides or attach on same side Membrane: membranous structure almost occluding the entire diameter of the vein Malformed valve: dysdynamic or fibrous valve Stenosis: CSA measurement of $\leq 3 \text{ mm}^2$ Annulus: circumferential thickened vein wall that is restricting the vein from fully expanding with respiratory or positional changes Reflux/bidirectional flow: present in the IJV for >0.88 seconds with the head at 90° and 0° Paradox: vein wall not reacting to respiratory phase; noncompliant No flow: no color flow noted in vein, despite deep breaths
Extraluminal structural venous abnormality; this is a restriction of the venous wall or stenosis; these abnormalities include stenosis and annulus	
Functional venous abnormality; this is an abnormal cerebral venous outflow in the presence of a structural venous anomaly; these abnormalities include reflux/bidirectional flow, paradox, and no flow	

Note:—CSA indicates cross-sectional area.

Table 2: Demographic and clinical characteristics in patients with MS and HCs^a

	MS (<i>n</i> = 150)	HC (<i>n</i> = 63)	<i>P</i>	NPRMS (<i>n</i> = 104)	PRMS (<i>n</i> = 46)	<i>P</i>
Female sex (No.) (%)	102 (68)	36 (57.1)	NS	73 (70.2)	29 (63)	NS
Age (yr) (mean) (SD)	43.2 (10.6)	42 (15)	NS	40.7 (10.7)	48.6 (8.2)	<.001
Age at onset, mean (SD)	31.3 (10)	—	—	31.9 (9.9)	30 (10.3)	NS
Disease duration (mean) (SD)	12.1 (9.1)	—	—	9.2 (7)	18.6 (9.9)	<.001
Disease course (No.) (%)		—				
RR	104 (70.4)			104 (100)		
SP	38 (25.3)				38 (82.6)	
PP	8 (5.3)				8 (17.4)	
EDSS (mean) (SD) (median)	3.4 (9.1) 2.5	—	—	2.5 (1.4) 2.0	5.8 (1.7) 6.0	<.001

Note:—NS indicates nonsignificant; NPR, nonprogressive; PR, progressive; —, not available.

^a The differences between the study groups were tested using the χ^2 test, Student's *t* test, and Mann-Whitney U test.

All MRV scans were examined by 2 independent neuroradiologists in a blinded manner (D.H. and K.D.). The reproducibility results were previously reported.¹³

Statistical Analyses

Statistical analysis was performed by using the Statistical Package for the Social Sciences (Version 16.0; SPS, Chicago, Illinois). For descriptive statistics and estimates of prevalence and number of venous abnormalities, *t* tests, Fisher exact tests, and the Mann-Whitney *U* tests were used. Reproducibility was calculated by using the Cohen κ and ICC tests. The relationship between different DS and MRV venous characteristics was assessed by using the Spearman rank correlation. Patients with MS were further divided into 2 groups: MS nonprogressive (RR) and MS progressive (SP and PP).

To correct for multiple comparisons, the nominal *P* value $<.01$ was considered as significant by using 2-tailed tests.

Results

Demographic and Clinical Characteristics

Table 2 shows demographic and clinical characteristics of patients with MS and HCs. As expected, patients with progressive MS had significantly higher age and EDSS scores and longer disease duration than patients with nonprogressive MS (all $P < .001$). Of the 150 patients with MS, 95 (63.3%) were on disease-modifying therapy.

Reproducibility Results

On-line Tables 1 and 2 show the intra- and inter-rater reproducibility for DS parameters. There was modest-to-high intra-rater agreement for depicting total intra- and extraluminal structural and functional venous abnormalities. However, there was low-to-moderate inter-rater agreement for the assessment of intraluminal and functional venous abnormalities and modest-to-high inter-rater agreement for the assessment of the extraluminal abnormalities.

Intraluminal and Extraluminal Structural and Functional Venous Abnormalities in IJVs, as Evidenced by Doppler Sonography

Table 3 shows the individual frequency and number of intra- and extraluminal structural and functional IJV abnormalities, as evidenced by DS. Significantly more patients with MS presented with total ($P = .004$) and intraluminal ($P = .008$) structural and functional ($P = .003$) abnormalities, with a trend toward more extraluminal abnormalities compared with HCs ($P = .044$). There was a significantly higher number of total ($P = .001$) and intraluminal structural ($P = .005$) and functional abnormalities ($P < .0001$), with a trend for a higher number of extraluminal structural ($P = .023$) abnormalities in patients with MS compared with HCs. In patients with MS, there was a significant relationship between the higher number of intraluminal and functional abnormalities ($r = 0.36$,

Table 3: Intraluminal and extraluminal structural and functional venous abnormalities in IJVs in patients with MS and HCs on DS^a

Individual Frequency of Venous Abnormalities	HC (n = 63)	MS (n = 150)	P Value ^b	NPRMS (n = 104)	PRMS (n = 46)	P Value ^c
Total structural (No.) (%)	34 (54)	111 (74)	.004	72 (69.2)	39 (84.8)	.033
Intraluminal structural (No.) (%)	31 (49.2)	102 (68)	.008	67 (64.4)	35 (76.1)	.110
Web	0	6 (4)		5 (4.8)	1 (2.2)	
Flap	17 (27)	51 (34)		36 (34.6)	15 (32.6)	
Septum	9 (14.3)	43 (28.7)		34 (32.7)	9 (19.6)	
Membrane	0	0		0	0	
Malformed valve	18 (28.6)	40 (26.7)		25 (24)	15 (32.6)	
Extraluminal structural (No.) (%)	7 (11.1)	33 (22)	.044	17 (16.3)	16 (34.8)	.01
Stenosis	7 (11.1)	33 (22)		17 (16.3)	16 (34.8)	
Annulus	0	0		0	0	
Total functional (No.) (%)	21 (33.3)	82 (54.7)	.003	55 (52.9)	27 (58.7)	.316
Reflux	20 (31.7)	74 (49.3)		49 (47.1)	25 (54.3)	
Paradox	0	2 (1.3)		1 (1)	1 (2.2)	
No flow	2 (3.2)	16 (10.7)		8 (7.7)	8 (17.4)	
No. of venous abnormalities						
Total structural (mean) (SD)	1.05 (1.3)	1.85 (1.8)	.001	1.75 (1.7)	2.04 (1)	.384
Intraluminal structural (mean) (SD)	0.9 (1.2)	1.53 (1.7)	.005	1.5 (1.6)	1.61 (1.9)	.805
Web	0	0.07 (0.4)		0.07 (0.3)	0.09 (0.6)	
Flap	0.33 (0.6)	0.56 (1)		0.56 (1)	0.57 (1)	
Septum	0.24 (0.7)	0.55 (1)		0.57 (1)	0.5 (1.2)	
Membrane	0	0		0	0	
Malformed valve	0.35 (0.6)	0.37 (0.7)		0.33 (0.6)	0.5 (0.8)	
Extraluminal structural, (mean) (SD)	0.13 (0.5)	0.31 (0.7)	.023	0.25 (0.7)	0.43 (0.7)	.01
Stenosis	0.13 (.5)	0.31 (0.7)		0.25 (0.7)	0.43 (0.7)	
Annulus	0	0		0	0	
Total functional (mean) (SD)	0.51 (0.9)	1.13 (1.2)	<.0001	1.02 (1.2)	1.4 (1.3)	.096
Reflux	0.44 (0.8)	0.88 (1.1)		0.85 (1.1)	0.96 (1.2)	
Paradox	0	0.02 (0.2)		0.02 (0.2)	0.02 (0.1)	
No flow	0.06 (0.6)	0.17 (0.5)		0.13 (0.5)	0.26 (0.6)	

Note:—NPR indicates nonprogressive; PR, progressive.

^a The frequency differences of the structural and functional venous abnormalities between the study groups were tested using the Fisher exact test, whereas the number of venous abnormalities differences was tested using Mann-Whitney U test.

^b P value represents comparison between HC and MS.

^c P value represents comparison between patients with NPR- and PRMS.

Table 4: Flow morphology of IJVs in patients with MS and HCs 2D-TOF using venography and 3D-TRICKS^a

Morphology Score	TOF				TRICKS	
	HC (n = 63)	MS (n = 150)	NPRMS (n = 104)	PRMS (n = 46)	NPRMS (n = 96)	PRMS (n = 44)
Absent (No.) (%)	5 (7.9)	23 (15.3)	14 (13.5)	9 (19.6)	7 (6.7)	2 (4.3)
Pinpoint (No.) (%)	12 (19)	23 (15.3)	12 (11.5)	11 (23.9)	18 (17.3)	17 (37)
Flattened (No.) (%)	18 (28.6)	50 (33.3)	33 (31.7)	17 (37)	43 (41.3)	30 (65.2)
Crescentic (No.) (%)	2 (3.2)	2 (1.3)	2 (1.9)	0 (0)	3 (2.9)	1 (2.2)
Ellipsoidal (No.) (%)	26 (41.3)	52 (34.7)	43 (41.3)	9 (19.6)	93 (89.4)	41 (89.1)
P value		.259		.006		.01

Note:—NPR indicates nonprogressive; PR, progressive.

^a The differences on the ordinal morphologic flow scale between the study groups were evaluated using the Mann-Whitney U test. Only absent and pinpoint flows in the IJVs were considered abnormal.

$P = <.0001$), extraluminal and functional abnormalities ($r = 0.29$, $P = .008$), and intraluminal and extraluminal abnormalities ($r = 0.23$, $P = .006$).

There were significantly more patients with extraluminal structural abnormalities ($P = .01$) and a higher number of extraluminal abnormalities ($P = .01$) in patients with progressive MS compared with those with nonprogressive MS. There was also a trend toward more patients with total structural abnormalities ($P = .033$). No significant differences were observed between patients with progressive and nonprogressive MS for intraluminal structural and functional abnormalities.

No significant relationship was found in patients with MS or HCs between age and sex, and the frequency and number of structural and functional IJV abnormalities, except a trend

toward greater age and a higher number of functional IJV abnormalities in patients with progressive MS ($r = 0.33$, $P = .026$).

MRV Findings in IJVs

Table 4 shows MRV findings in patients with MS and HCs on TOF and in progressive and nonprogressive MS subgroups on TOF and TRICKS MR imaging sequences. No significant differences were found on the flow-morphologic scale between patients with MS and HCs. Abnormal TOF findings (absent/pinpoint flow morphology) were found in 46 (30.7%) of the patients with MS and 17 (27%) HCs.

Significantly more abnormalities were observed on the flow-morphologic scale in patients with progressive compared

with nonprogressive MS on TOF ($P = .006$) and TRICKS ($P = .01$). In total, 20 (43.5%) patients with progressive MS had abnormal findings on TOF, and 19 (43.2%), on TRICKS. The figures were 26 (25%) in patients with nonprogressive MS for TOF and 25 (26%) for TRICKS. The relationship between TOF and TRICKS findings was highly related ($r = 0.95$, $P < .001$).

Collateral Vein Findings

There was a trend toward a higher mean number of collateral veins in patients with MS compared with HCs on TOF (2.56 versus 2.1, $P = .016$). No significant differences were observed in the number of collateral veins between patients with progressive and nonprogressive MS on TOF (2.65 versus 2.52, $P = .715$) or on TRICKS (2.57 versus 2.62, $P = .756$).

Patients with MS with a higher number of functional and intraluminal IJV DS abnormalities showed a significantly higher number of collateral veins on TRICKS ($r = 0.27$, $P = .009$ and $r = 0.23$, $P = .01$, respectively) and on TOF ($r = 0.27$, $P = .006$ and $r = 0.22$, $P = .01$, respectively).

VV Findings

There was absent flow in the VVs of 6 (9.5%) HCs and of 16 (10.7%) patients with MS on DS ($P = .932$). No significant differences were observed between patients with progressive and nonprogressive MS in VV flow on DS and MRV.

Discussion

This study investigated the intra- and extraluminal structural and functional extracranial venous abnormalities and the potential value of MRV and DS in depicting those abnormalities. Patients with MS showed a significantly higher number of total and intraluminal structural and functional abnormalities on DS compared with HCs. No differences on the morphologic MRV flow scale were found between patients with MS and HCs. Patients with progressive MS presented with significantly more extraluminal DS abnormalities and more flow abnormalities on MRV than those with nonprogressive MS.

From the time it was first mentioned, the CCSVI theory has not ceased to provoke controversy and attention in the scientific community²⁰⁻²³ and the media. The originally reported sensitivity and specificity of the CCSVI criteria for MS diagnosis⁵ were not reproduced by recent DS,⁶⁻¹⁰ MRV,¹¹⁻¹³ or CV^{14,15} studies. A major point that can explain different findings between the original and subsequent studies is that the CCSVI diagnosis is mainly based on extra- and transcranial echo-color DS criteria, which are operator-dependent and not easy to blind in a clinical setting. Moreover, the value of the CCSVI criteria is controversial because they combine functional and structural intra- and extracranial venous abnormalities in a single binary composite.²⁴ The assessment of the second CCSVI criterion (reflux in deep cerebral veins) is particularly controversial because the direction of the blood flow in veins connecting cortical with deep veins may vary considerably as a consequence of the physiologic interindividual variation of the cerebral venous anatomy.^{6,7,9,24} In addition, the value of MRV-based techniques for a diagnosis of CCSVI has not yet been completely elucidated.^{13,25} To provide better evidence on the types of venous anomalies, we focused, in this study, on the assessment of extracranial neck veins by

2 different noninvasive imaging techniques. Furthermore, we divided venous abnormalities into structural (intra- and extraluminal) and functional, to better understand their contribution to the CCSVI concept.

The DS examination showed that a substantial number of patients with MS and HCs presented with at least 1 structural venous abnormality in their IJVs. Similar results were found for the number of intraluminal abnormalities in the IJVs. More patients with MS and HCs presented with intraluminal abnormalities compared with the extraluminal ones. Of all the intraluminal abnormalities examined, the septum and flap occurred most frequently in patients with MS as well as in HCs, while no difference between the groups was found for the malformed valve (impaired mobility or thickened fibrotic valve), in line with a recent report.⁹ No membrane abnormalities were found in patients with MS and HCs.

All in all, these results suggest that the most frequent venous abnormalities in the IJVs, indicative of CCSVI, are of intraluminal origin. Although head and neck veins are clearly shown by using MRV, this technique does not have the resolution to visualize intraluminal abnormalities. This is 1 of the main limitations when comparing MRV with DS, as discussed in a recent multimodal diagnostic study.²⁵ The fact that intraluminal abnormalities present the most frequent type of venous abnormality in the CCSVI criteria^{5,6,10} can further explain the discrepant results between DS^{5,6} and MRV studies.¹¹⁻¹³ Although our intrarater reproducibility results showed modest-to-high agreement for the detection of the type and number of intraluminal abnormalities, the inter-rater agreement for these abnormalities showed low reproducibility for the detection of type and modest reproducibility for the detection of number. In the present study, the presence of intraluminal abnormalities did not imply the presence of functional abnormality or significant IJV stenosis (cross-sectional area, $\leq 0.3 \text{ cm}^2$). Therefore, the results from this study suggest that HCs also present frequently with intraluminal abnormalities, as recently reported.^{6,10} The possible origin of these abnormalities could be congenital,²⁶ aging-dependent, or a possible consequence of an inflammatory process.⁶ Therefore, further research is needed to determine whether these anomalies represent a pathologic condition or a physiologic variation.

No significant intraluminal differences were seen in patients with progressive versus nonprogressive MS, which could indicate that intraluminal abnormalities may appear earlier in the disease process. However, we found that age in patients with progressive MS correlated with the presence of DS intraluminal abnormalities. Although we did not find a relationship between age and the number of intraluminal abnormalities either in HCs or in the entire MS group, it cannot be excluded that the prevalence of these abnormalities is aging-dependent. A recent study that investigated IJV changes with aging in HCs found a decreased proportion of venous drainage and increased IJV reflux prevalence in older subjects.²⁷

In the present study, a trend toward a higher prevalence and number of extraluminal abnormalities was found in patients with MS compared with HCs on DS, whereas more patients with progressive-versus-nonprogressive MS presented with those anomalies. The presence of an annulus was not detected, contrary to previously reported results.^{5,16} Both

intra- and inter-rater reproducibility showed modest-to-high agreement for the presence and number of extraluminal abnormalities. Therefore, our reproducibility data suggest that DS evaluation of extraluminal abnormalities is less operator-dependent and could be more reliable in the evaluation of the venous anomalies in the IJVs.

On DS, patients with MS showed a significantly higher prevalence and number of functional abnormalities in the IJVs than HCs. No differences were seen between patients with progressive and nonprogressive MS. The most prevalent abnormality was reflux in patients with MS and in HCs, followed by no flow. A recent study found a strong correlation between jugular venous reflux and age-related white matter changes in elderly healthy subjects.²⁸ Although a significant relationship was found between the number of functional and the number of intra- and extraluminal abnormalities, this relationship could explain, at best, only 20% of the variance. In addition, modest-to-high intrarater agreement for the detection of type and number of functional abnormalities was not observed for inter-rater agreement. More quantitative measures for the definition of functional abnormalities such as blood flow velocity and blood volume flow could be potentially more reliable in assessing the degree of venous outflow obstruction in the IJVs.⁷

An attempt was made to distinguish intra- versus extraluminal structural and functional abnormalities in the IJVs with both MRV techniques used in this study, but ultimately, this distinction was not possible.^{13,25} Consequently, all MRV abnormalities were classified as flow abnormalities due to possible intra- or extraluminal origin. No significant differences on the morphologic flow MRV scale were found between patients with MS and HCs, in line with 3 recently published smaller scale MRV venous flow studies.¹¹⁻¹³ In a recent study,¹³ modest-to-low scan-rescan reproducibility agreement between baseline and follow-up MRV was detected. Nevertheless, we found significantly more flow abnormalities in patients with progressive versus nonprogressive MS both on TOF and TRICKS, confirming the DS extraluminal results. One of the limitations in the present study is the use of conventional MRV techniques, which are more prone to artifacts compared with other more advanced approaches.^{12,29} Although we did not perform contrast MRV sequences in HCs as recommended by our institutional review board, we showed high correlation between TOF and TRICKS in the present and previous studies.^{25,30}

In the present study, there was a trend toward a higher number of collateral veins in patients with MS compared with HCs, contrary to our previous study.¹³ Patients with MS with a higher number of DS intraluminal IJV flow abnormalities showed a significantly higher number of collateral veins on both MRV sequences. No significant difference in the number of collaterals between patients with nonprogressive versus progressive MS was found. These results indeed provide an important finding, because they support the existence of collateral circulation as a possible compensatory mechanism for the higher number of functional and intraluminal abnormalities in the IJVs, as previously proposed.^{5,16} It could be hypothesized that collaterals develop as a compensatory mechanism for the presence of intraluminal structural flow abnormalities; and when their compensatory ability is overcome, extraluminal

abnormalities begin to develop. This theory is supported by recent work of Yamout et al,¹⁴ who performed CV on 42 patients with MS in various phases of the disease (at onset and after 5 and 10 years) and found that extracranial venous stenosis was very rare at onset but became more frequent in subjects with longer MS duration. We considered the use of DS for visualizing collaterals; however, due to Doppler inability to follow the complete course of the collateral vein, we were unable to identify the vein with 100% accuracy. Therefore, MRV is more accurate than DS for following and labeling collaterals of the extracranial venous system. In a majority of cases, there was also a correlation between the size of the ipsilateral IJV and collateral veins, meaning that prominent collaterals followed stenotic IJVs with no visible flow. However, there were cases with normal patent IJV lumens and prominent collaterals. If the IJVs are developmentally smaller, then the other veins would likely be more prominent. Longitudinal studies should investigate the evolution of collaterals in stenotic or developmentally smaller IJVs.

We did not find VV flow differences on MRV and DS between patients with MS and HCs or between MS subgroups, which is in line with recent studies.^{13,25}

The value of DS and MRV for screening of CCSVI was tested against CV with promising results in 2 recent pilot studies that included patients with MS and HCs.^{25,30} In 1 of these studies, DS showed 82% sensitivity, 100% specificity, and 99% positive and 95% negative predictive values compared with CV in 10 patients with MS.²⁵ However, another recent study found no overlap between CV and DS in 7 of the 8 patients who presented with a sonographic finding of CCSVI.⁹ A multimodal approach by using noninvasive and invasive diagnostic techniques is recommended to determine the degree of extracranial venous structural and functional impairment in patients with MS and HCs.

One of the limits of this study is that we did not use invasive CV to confirm the DS and MRV findings. Although CV is considered the criterion standard for assessing and grading endovascular stenoses, CV is merely lumenography, providing little or no data on the wall of the vessel or its intraluminal structures. Malformed and/or reversed valve cusps can be crossed by the catheter and kept open artificially, thereby preventing documentation of stenosis.²⁴ No established criteria or guidelines currently exist on CV for the detection of venous anomalies indicative of CCSVI.²⁴ Any venous lumen reduction >50% on CV is considered a sign of significant stenosis, which is somewhat arbitrary.^{5,16} More sophisticated CV categorical criteria (ranging from grade 1 to grade 4) were recently proposed.¹⁵ Our preliminary experience with CV^{25,30} indicates that proper training is needed for recognition of pathologic intraluminal anomalies indicative of CCSVI and that more sophisticated criteria for detection of these anomalies, such as time to empty contrast from veins or waisting of the balloon, need to be tested and validated.²⁴ In addition, CV is an invasive method that requires radiation exposure, and there are ethical concerns in applying this technique to a large group of HCs.

Another limitation of our study is that we did not measure directly the venous pressures and flow patterns in the dural venous sinuses (the common pathway out of the brain before the cervical veins) to demonstrate any evidence of increased

pressure or abnormal flow patterns, such as reflux or bi-directional flow. Additionally, because there are no indications that patients with sinus thrombosis and elevated intracranial pressures or those with jugular occlusions or resections (eg, with radical neck dissections) ever develop demyelinating lesions,²⁰ our DS and MRV findings need further evaluation.

Conclusions

Despite the limitations in comparing different imaging techniques and the use of different imaging criteria, we found that conventional MRV has limited value for detection of extracranial venous anomalies compared with DS because it cannot distinguish intraluminal structural and functional venous abnormalities. However, MRV is more sensitive for showing collaterals.

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