Screening for chronic cerebrospinal venous insufficiency (CCSVI) using ultrasound - Recommendations for a protocol

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Chronic cerebrospinal venous insufficiency (CCSVI) is a syndrome characterized by stenoses or obstructions of the internal jugular and/or azygos veins with disturbed flow and formation of collateral venous channels. Studies using ultrasound in patients with multiple sclerosis (MS) have demonstrated a high prevalence of CCSVI (mean 70%; range 0-100%; N.=1496), whereas, in normal controls and patients without MS the prevalence was much lower (mean 10%; range 0-36%; N.=635). Ultrasound uses a combination of physiological measurements as well as anatomical imaging and has been used for the detection of CCSVI by different centers with variable results. A high prevalence ranging from 62% to 100% of obstructive lesions has been found by some teams in patients with MS compared with a lower prevalence of 0-25% in controls. However, absence of such lesions or a lower prevalence (16-52%) has been reported by others. This variability could be the result of differences in technique, training, experience or criteria used. The current lack of a methodology shared among experts is a confounding element in epidemiologic studies, and does not permit further Bayesan or other kind of analysis. In order to ensure a high reproducibility of Duplex scanning with comparable accuracy between centers, a detailed protocol with standard methodology and criteria is proposed. This is also necessary for training. It has been shown that inter-rater variability increases post-training (from k=0.47 to k=0.80), while within-rater reproducibility in trained operators was k=0.75. Finally, the consensus document proposes a reporting standard of Duplex measurements, and future research to answer areas of uncertainty.

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Chronic cerebrospinal venous insufficiency (CCSVI) is a syndrome characterized by stenoses or obstructions of the internal jugular (IJV) and/or azygos (AZ) veins with disturbed flow and formation of collateral venous channels.[1, 2] Ultrasonic and venographic studies of the internal jugular and azygos venous systems in patients with multiple sclerosis (MS) have demonstrated a high prevalence of CCSVI (mean 70%; range 0-100%; N.=1040) associated with activation of collaterals. In contrast, ultrasonic and venographic examinations of normal controls and patients without MS have demonstrated a much lower prevalence (mean 10%; range 0-36%; N.=635) (Table I).[1-16]

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TABLE I. — *Prevalence of CCSVI in patients with MS and healthy controls**

Author(ref)	MS Patients		Controls		Investigation method
	CCSVI	Total	CCSVI	Total	
Zamboni *et al.*, 2009 [1]	65 (100%)	65	0	235	Duplex,Venography
Zivadinov *et al.*, 2011 [4]	162 (56.1%)	289	37 (22,7%)	163	Duplex
Doepp *et al.*, 2011 [8]	0 (0%)	56	0 (0%)	20	Duplex
Mayer *et al.*, 2011 [9]	0 (0%)	20	1 (5%)	20	Duplex
Yamout *et al.*, 2010 [10]	19 (45%)	42	—	—	Venography
Baracchini *et al.*, 2011 [11]	8 (16%)	50	1 (2%)	50	Duplex, Venography
Al Omari *et al.*, 2010 [5]	21 (84%)	25	0 (0%)	25	Duplex
Simka *et al.*, 2010 [6]	64 (91%)	70	—	—	Duplex
Bastianello *et al.*, 2011 [7]	610 (86%)	710	—	—	Duplex
Marder *et al.*, 2011 [16]	0 (0%)	18	0 (0%)	11	Duplex
Centonze *et al.*, 2011 [14]	42 (50%)	84	20 (36%)	56	Duplex
Zamboni *et al.*, 2011 [32]	18 (100%)	18	6 (0%)	6	Duplex, Venography
Zaharchuck *et al.*, 2011 [8]	21 (54%)	39	—	39	Venography, MRV
Zivadinov *et al.*, 2011 [3]	10 (100%)	10	—	10	Duplex, Venography
TOTAL	1040 (70%)	1496	65 (10%)	635	

*These studies are heterogeneous because compare controls with different categories of MS patients, clinically isolated syndrome and also other neurological diseases. In some cases studies were performed with unblinded methodology and not trained operators.

The origin of venous anomalies is still not completely understood. Such lesions consist mostly of segmental hypoplasia or intraluminal defects, collectively classified as truncular venous malformations (VM).[17-19] Truncular lesions are the result of developmental arrest that occurs during the "later" stages of vascular trunk formation in fetal life. Immature or incomplete development of the main axial veins result in aplasia, hypoplasia or hyperplasia of the vessel or as a defective vessel with obstruction from intraluminal lesions (*e.g.*, vein web, spur, annulus, or septum) or dilatation (*e.g.*, jugular vein ectasia/aneurysm). Such lesions were not detected in radiological studies on healthy subjects;[20-29] to the contrary CCSVI-like lesions were described associated to disabling myelopathies.[30, 31]

The increased prevalence of obstruction to the drainage of cerebrospinal veins in patients with MS suggests that venous obstruction may be a contributory factor in the development and progression of the disease. It has also been suggested that relief of such obstruction may produce clinical benefit. In two observational studies, overall involving 80 MS patients with CCSVI, angioplasty reduced the rate of relapse, improved the Multiple sclerosis Functional Composite in patients with relapsing remitting MS,[32, 33] and improved physical and mental QOL in relapsing remitting and primary progressive MS.[32] In another study of 31 patients followed for twelve months, angioplasty reduced chronic fatigue as assessed by the Fatigue Severity Scale and the Fatigue Impact Scale.[34] Safety was confirmed in more than 1000 procedures.[35, 36] However, the true clinical benefit will be only known when the results of multicenter studies, now in progress, become available. For a list of clinical studies in progress please see Appendix 1.

Results from preliminary pilot studies cannot support a role for the endovascular treatment of CCSVI in MS patients outside of approved clinical trials. The Faculty feels that current evidence for the association between CCSVI and MS completely justifies performance of blinded, randomized, controlled clinical trials that will assess the benefits of endovascular interventions according to established clinical, MRI and/or quality-of-life treatment outcomes. Moreover, only safe and ethical approaches should be encouraged in designing new prospective clinical trials that will investigate clinical outcomes by the means of independent assessors, and/or blinded MR measures. The latter are not affected by any placebo effect. This may rapidly provide rapidly a large amount of data for meta-analysis, and possibly for an international registry.

Catheter venography (CV) is considered to be the gold standard for determining the anatomical site, type and extent of lesions producing cerebrospinal venous insufficiency (CCSVI).[3, 9] However, CV is invasive and cannot be used as a screening method. Despite being considered the 'gold standard' for assessing and grading

endovascular stenoses, catheter venography is merely lumenography providing little data on the wall or the presence of intraluminal defects. Therefore, in cases where only the intraluminal venous abnormalities are present, it is extremely difficult to measure the degree of stenosis by CV. In addition, malformed and/or reversed valve cusps can be crossed by the catheter and kept open artificially, thereby preventing documentation of stenosis. However, CV can be complemented by the use of more sophisticated criteria, such as time to empty contrast from vein or wasting of the balloon. In contrast, ultrasound is an ideally suited noninvasive method of screening and could become a valuable diagnostic test when high sensitivity and specificity is demonstrated. In the presence of high sensitivity and specificity, venography will only be needed when a decision has already been made for intervention.

Ultrasound in the form of Duplex scanning uses a combination of physiological measurements as well as anatomical imaging and has been used for the detection of CCSVI by different centers with variable results. A high prevalence ranging from 62% to 100% of obstructive lesions has been found by some teams in patients with MS, compared with low prevalence of 0-25% in controls.[1-9] However, absence of such lesions or a lower prevalence (16-52%) has been reported by others.[10-16] This variability could be the result of differences in technique, training, experience or criteria used.

In order to ensure a high reproducibility of Duplex scanning with comparable accuracy between centers, a detailed protocol with standard methodology and criteria is needed. A detailed protocol is also necessary to plan a proper training program. It has been shown that inter-rater variability increases post-training (in non-trained operators it was k=0.47 and in trained operators it was k=0.80).[37] Within-rater reproducibility for CCSVI status was assessed on 28 subjects who were examined in a blinded manner twice over a one-week period and the agreement was 89.3% between the two measurements (k=0.75).[4] Also, standardization of the method of reporting of Duplex measurements and other findings will facilitate validation of the proposed criteria by different centers (Appendix 2).

The aim of this document was to produce recommendations for such a protocol and indicate what future research is needed to answer areas of uncertainty.

Anatomy of cerebrospinal venous system

The cerebrospinal venous system is usually asymmetric and has a more variable vessel pattern than the arterial system. The intracranial part is mainly composed of parenchymal veins draining into the dural sinuses. Two main systems are responsible for blood collection, the superficial (cortical) system (blood reaches dural sinuses by cortical veins and drains blood mainly from cortex and part of subcortical white matter), and the deep cerebral venous system, composed of internal cerebral veins, basal vein of Rosenthal and the great cerebral vein of Galen and their tributaries. They drain the deep "periventricular" white and central gray matter "basal ganglia and thalamus" surrounding the lateral and third ventricles, the brain stem and anterior cerebellum which drains to the straight sinus.[2, 38] Blood is collected by the dural sinuses and directed towards the main extracranial venous outflow routes: the internal jugular vein (IJV) and the vertebral system. The IJV drains into the superior vena cava via the brachiocephalic vein (Figure 1). The vertebral venous system is a valveless system stretching throughout the length of the entire spinal column and is made of three parts: internal intraspinal part, epidural veins, and extraspinal paravertebral part. The extraspinal part in the neck consists of the vertebral veins (VV) which accompany the vertebral artery and drain into the innominate vein on the right and into the subclavian vein on the left (Figure 1A). They are reported to be valveless but venographic studies have shown that valves may be present at the junction of the vertebral and subclavian veins. The rest of the vertebral venous system which is a rich plexus communicates with the deep thoracic and lumbar veins, intercostal veins, the azygos and hemiazygos veins. The lumbar hemiazygos arch is connected with the left renal vein representing a major outflow route for shunting blood into the inferior vena cava. The azygos vein represents the final collector and drains into the superior vena cava with an outlet on the posterior aspect just one cm below the brachiocephalic trunks [17] (Figure 1B).

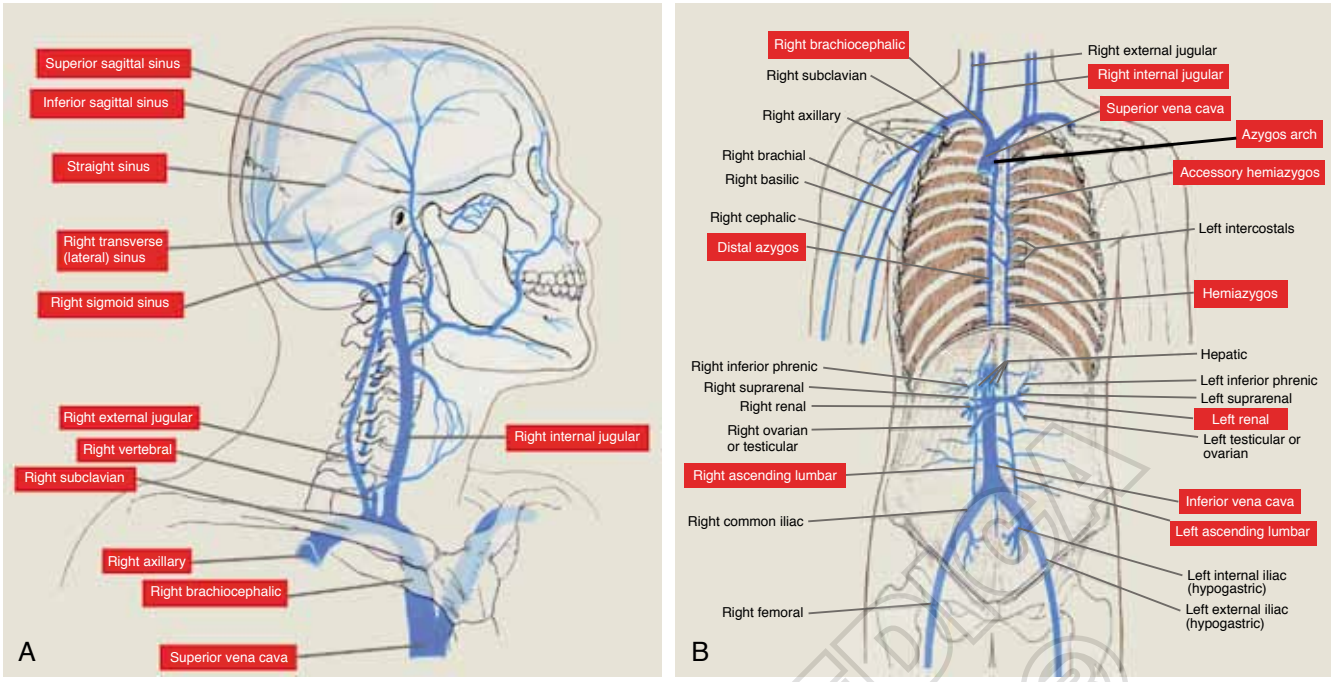

Figure 1.—Anatomy of the cerebrospinal venous system.

Figure 2.—Upper IJV level (J3).

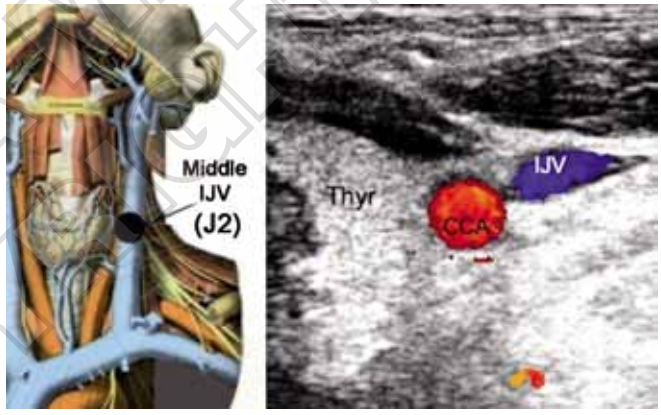

Figure 3.—Middle IJV level (J2).

Ultrasonographic anatomy of the cerebrospinal venous system

The IJV can be subdivided into three extracranial venous segments: upper (J3), middle (J2), and lower (J1) (Figure 2). The middle segment is adjacent to the thyroid gland (Figure 3), and is the segment between the entry of the common facial vein and the beginning of the last 2 cm of the IJV (Figure 4). The IJV can be insonated easily at all three levels. The VV can be easily insonated at all levels, but more easily between the transverse processes of the 5th and 6th cervical vertebrae.

Pathophysiology of cerebrospinal venous system and CCSVI

Blood leaves the brain because of the residual propulsion of the arterial pressure (*vis a tergo*), complemented by respiratory mechanisms (*vis a fronte*).[38-40] The latter consists of the thoracic pump which produces a negative intrathoracic pressure during inspiration increasing the aspiration of blood towards the right atrium. In addition to the *vis a tergo* and *vis a fronte*, changes in posture and gravity

play a main role in ensuring a correct cerebral venous return.[37-45].

In the horizontal position, the predominant cerebral venous outflow is through the IJVs, whereas in the upright position the VVs become the predominant pathway. This has been demonstrated by angiographic studies and cerebral blood flow measurements using nitrous oxide, labeled erythrocytes and thermodilution techniques and more recently by volume flow measurements using Duplex scanning (Appendix 3).[38-43] When the subject is upright there is a gradient of about 30 mmHg between the parenchymal veins and the jugular vein at the base of the neck, and the hydrostatic pressure is negative.[41] In contrast when the subject lying supine there is a redistribution of blood in the venous system due to the lack of the hydrostatic gradient, and the IJV becomes enlarged.[38-43] In the study of Doepp *et al*.[44] a predominant non-jugular drainage pattern in the supine position was found in only 6% of healthy volunteers.

As defined above, CCSVI is characterized by stenoses of the internal jugular and/or azygos veins which are shown by B-mode ultrasound to be mostly intraluminal defects.[1-8, 45, 46] These stenoses are associated with the development of collateral veins indicating insufficient drainage. Moreover, in course of CCSVI, no change in CSA has been found passing from the supine to the upright position, suggesting the obstruction of the main outflow route and scarce flow through the collaterals. In some studies a paradoxical increased CSA of the IJV in upright as compared to supine position was observed.[1, 3, 4, 7, 8, 45] Moreover, the impairment in MS patients of the favorable hydrostatic gradient in upright position has been measured by Doppler flowmetry: the authors demonstrated a much larger change in blood flow volume in normal subjects compared to MS patients when the subjects move from a supine to an upright position. A change of 128 mL/min and 56 mL/min for the right and left sides, respectively, for MS patients was detected, but a much larger change of 266 mL/min and 105 mL/min for their normal subjects was found.

All these studies strongly support the loss of the physiological postural mechanism of cerebral venous outflow in the presence of CCSVI. Possible causes include intraluminal septum, membrane, and immobile valve affecting the hydrostatic pressure gradient in the upright position.[10]

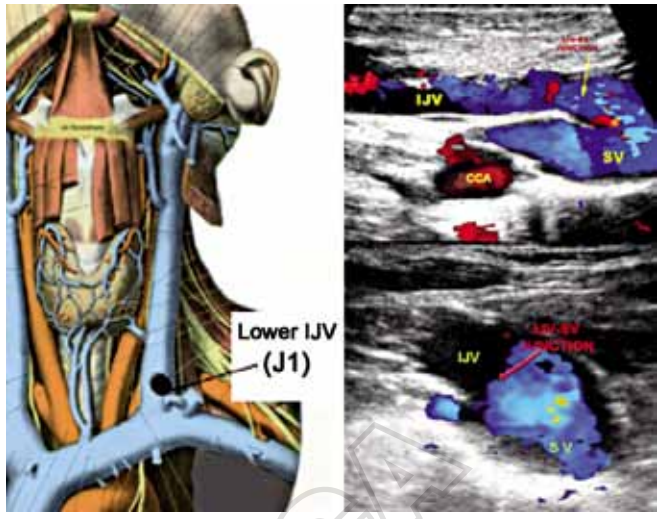

Figure 4.—Lower IJV level (J1).

While the relationship between CCSVI and MS is not well understood, related work has revealed that extracranial venous obstruction is implicated in brain pathophysiology, especially about venous pressure, perfusion and CSF dynamics:

1) data on venous pressure are few and controversial. A group of investigators indirectly measured, by the means of ophthalmod, the intracranial venous pressure in MS patients, healthy controls, and patients with elevated intracranial pressure. They found no evidence of increased intracranial pressure in MS.[47] In contrast, a significant transtenotic gradient of 2.2 cmH_2O has been found out in patients who underwent catheter venography for CCSVI and MS.[32] In addition, the Beggs analysis of the Doepp *et al*.'s data suggests that venous hypertension might be a feature of MS.[10, 48] According to this analysis, Doepp's flow measurements implies that in the MS patients there must have been an increase in pressure in the venous sinuses, and possibly also in the cerebral veins;

2) perfusion of brain parenchyma has been studied with MRI to assess cerebral blood flow, blood volume and the mean transit time from the arterial to the venous side of the cerebral circulation. In patients with MS, there is evidence that the cerebral blood flow is reduced and the mean transit time increased suggesting abnormalities at the microcirculation level.[49, 50] A neg-

ative linear relationship between cerebral blood flow measured with MRI perfusion techniques and the Doppler Venous Hemodynamic Insufficiency Severity score (VHISS) has been demonstrated [50] (Appendix 4). The latter has been used to assess the hemodynamic severity of CCSVI.[7, 50, 51] Thus, there seems to be a relationship between the severity of extracranial hemodynamic abnormalities and perfusion within the brain parenchyma.[51-53] There is a general agreement on global reduced perfusion of the brain in course of MS, something that cannot be related to an autoimmune process;[52]

3) in MS a significant reduction of the CSF flow was found.[51] The alteration of the dynamics of the CSF system in MS patients suggests that venous drainage abnormalities may be implicated in the pathophysiology of MS. The authors hypothesized that venous obstruction increases transmural pressure at the level of the superior saggital sinus. This may reduce CSF reabsorption, thereby reducing the CSF flow.[7, 48, 51]

CCSVI disturbs the normal postural and respiratory mechanisms of cerebral venous return resulting in an abnormal flow.[1-9] Thus, in CCSVI, the main extracranial cerebrospinal veins are obstructed, with venous flow being deviated into collaterals.[2, 48] The main collateral pathways activated are the condylar venous system, pterygoid plexus, and thyroid veins, anterior jugular veins and external jugular veins.[2]

Five main patterns in the distribution of significant (>50%) venous stenoses have been found in large venographic series of patients with MS:[1, 35]

— single jugular lesion (30-36%): a significant stenosis in one of the two IJVs with a compensatory enlargement of the contralateral IJV. This pattern was described just in one of the two venographic surveys.[35] No data are available concerning VV lesions;

— double jugular lesion (14-56%): bilateral stenoses of IJVs, with normal AZ venous system;

— double lesion (23%) involving one of the IJV and the proximal AZ vein;

— treble lesion (3-38%): significant stenosis of both IJVs and proximal AZ vein;

— multilevel involvement of AZ and external vertebral plexus, including the lumbar venous system (18%). Stenosis of IJVs is observed in approximately half of these patients, causing additional obstruction.[1]

A venographic grading system of obstructive lesions has been suggested by one group based on a series of 564 patients. Stage I consists of outflow delay without reflux towards the brain; stage II-outflow delay with mild reflux and/or prestenotic dilatation of the vein; stage III-outflow delay with reflux and outflow through collaterals; stage IV-no outflow through the vein with huge outflow through collaterals.[35]

Technique of Duplex scanning for CCSVI

Equipment and presets

Ideally, a sophisticated Duplex scanning system with a linear array broad bandwidth transducer suitable for vascular imaging such as the carotid artery can be used. Frequency ranges will vary according to the system and its application (*e.g.*, 7-5 MHz, 9-3 MHz, 10-5MHz). When visualization of the lower IJV segment (J1) proves technically challenging, the use of a curvilinear/microconvex probe with a smaller footprint may be useful. For TCD a phased array transducer should be used with a lower frequency bandwidth – for example, 1.5-2 MHz or 2-3 MHz.

A large number of instrumental settings affect the B-mode, color- and Doppler images on ultrasound. However, most manufacturers have chosen default values for these various settings that are preprogrammed for particular clinical applications. It is recommended to activate the system's venous presets initially and alter these starting values as required for each patient, according to the individual pathology.

Venous velocities are much lower than arterial velocities, so for color-Doppler imaging discrepancies are likely to occur. A number of technical considerations that should help achieve reproducibility are listed below.

Color flow

Pulse repetition frequency (PRF)

This is actually preset and it is related to the expected venous velocities. However, this may need to be lowered in order to detect lower flows or increased to avoid aliasing when the actual

velocities appear higher than predicted. Newer systems may not have a PRF control but may be controlled by the color "scale". The consensus suggests starting the investigation of the IJV with a PRF of 1.4 KHz to avoid aliasing.

Steering angles

To ensure complete color filling of the vessel under examination (if indeed flow is present) one must optimize the color-Doppler angle of insonation. This can be done and is generally practiced using a combination of probe angulation (particularly in transverse plane scanning) and color box steering. This is done in order to avoid an ultrasound beam perpendicular to the vessel which in turn would lead to no Doppler signal. Therefore, one must always steer the color box in a variety of directions in relation to the longitudinal planes of the B-mode image. When in transverse plane the color box must remain at 0 with only probe angulation being used to create the necessary angles.

Color gain

It is universally accepted that arterial flow is conventionally displayed red and venous flow blue. The gain control may need to be adjusted for each clinical setting. If set too low there may be incomplete color filling of the vessel of interest; if set too high one will see color outside the vessel and "noise" throughout the image.

Color wall filter

Color wall filter selection is important to optimize detection of low velocity.

Focal zones

Ideally this must be set to the region of interest. In color mode normally one focal zone exists (due to frame rate issues) and this may be preset for the image center. Focal zone can be manually adjusted so one should be prepared to alter where appropriate.

Persistence/frame averaging

Most modern systems have automated frame averaging. For example, when velocities are low, persistence will be high making pulsatile flow in veins harder to detect. It is important to keep the color box width and depth to the region of interest as this will result in the best/high frame rate.

Spectral Doppler

Pulse repetition frequency (PRF)

This will be preset as per manufacturer's values for a venous setting, but similar to color flow, clinical situations may arise that require the operator to alter these values to ensure an optimum Doppler spectral display. Set too high the slower-moving blood will not be displayed across the spectral display. Therefore one should set the Doppler PRF so that the resultant spectral waveform fills the display without aliasing the scale.

Focal depth

Normally, focal depth is set automatically to follow the sample volume but if not it should be adjusted manually.

Positioning of sample volume and angle of insonation

When examining venous flow the sample volume must be placed in the center of the vessel under examination. However, to include full range of velocities, including all areas of reflux in the vein, the gate needs to be open completely for entire lumen.

Ideally, the angle of insonation of the Doppler beam to the direction of flow should be 60° to keep the errors of absolute velocity measurements to a minimum. However, because this may be difficult to achieve in the IJV and VV without applying pressure on the skin by changing the angle of the probe, reducing the angle down to 45° is acceptable. Never go above 60°. Irrespective of the width of the gate, the cursor in the middle of the Doppler gate should be placed in the middle of the vessel and parallel to the flow axis.

Patient positioning and technical aspects of ultrasound examination

The CCSVI examination should be performed with the patient in both supine and sitting po-

sitions while breathing normally, with starting the examination in supine position. A tilting chair is advisable in order to avoid muscular contractions while changing position. As previously mentioned, each one of these positions is associated with a different outflow route.[38-45] The patient has to be comfortably positioned on an electro-mechanical chair or a standard examination table. After changing position, an adaptation period of at least 2 minutes should be allowed before any measurements are made. More than one posture change from supine to sitting and *vice versa* should be avoided, so as not to perturb the distribution of blood volume. A sufficient level of hydration within the twelve hours before the examination has to be recommended just to ensure the patient is not fasted.

We recommend that the subject breathes normally and where possible through the nose. This allows activation of the thoracic pump without undesirable muscle contraction in the neck. Also, this reduces contraction of the thoracic muscles reducing artifacts, especially when examining the lower section of the IJV (J1). The pump activation allows the assessment of flow direction. The cross-sectional area (CSA), and the flow direction, are measured at the end of the expiratory phase ensuring that it is after the activation of the thoracic pump.

The examiner should pay attention to the inclination of the patient's neck and appropriate means of neck support to avoid neck flexion, hyperextension or rotation to the left or right. This will avoid erroneous measurements of CSA and allow better visualization of the IJV when the patient is in the sitting position.

The operator should use appropriate arm support (especially when the patient is in the sitting position) in order to avoid strain to the arm, hand, wrist, back or shoulder. A pillow across the patient's chest, where the operator can rest the elbow whilst scanning, will provide good support. The problem of shoulder and arm fatigue is particularly significant when the examination is performed with the patient in the sitting position.

Use a large amount of ultrasonic gel to ensure complete coupling between the transducer and the patient's skin avoiding black cones and dark areas on the image. Also, a thick layer of ultrasonic gel avoids excessive pressure on the patient's neck that may change the shape and dimension of the IJV. Practical maneuvers that may help control the pressure of the transducer against the skin include: placing the ring or little finger on the thyroid cartilage in order to ensure better control of applied pressure.

How to perform CCSVI examination of internal jugular veins (supine and sitting position)

The investigation of the cerebrospinal venous return has to be performed with the patient really at rest. The patient needs to be calm, not agitated, to not alter the heart rate, with use of deep breathing technique. Evaluation begins with the patient in supine position.

B-mode evaluation

Perform a B-mode evaluation of the IJV with the linear array transducer in the transverse position (with respect to the IJV itself) from the base of the neck to the angle of the jaw. Although routine Valsalva maneuver is not recommended for CCSVI evaluation, there may be times when it may help visualize the IJV, especially with the patient in the sitting position, because normally in this position the cross-sectional area is at its smallest, or because of CCSVI, the IJV is sometimes completely collapsed. If a lumen can be opened by Valsalva it means that the lumen is normal. If a lumen cannot be opened by Valsalva, it could be suggestive of hypoplasia or agenesis of the IJV.

The Faculty recommends to perform Valsalva manoeuver at the end of the examination to check for agenesis especially if no flow is noted in the upright position. Performing Valsalva at the end of the examination avoids redistribution of blood volume, which may affect the entire investigation.

After evaluation in transverse plane, the IJV has to be completely evaluated in the longitudinal plane.

Valve abnormalities on B-mode

A valve is usually present at the termination of the IJV just before its junction with the subclavian vein. Valves of the lower por-

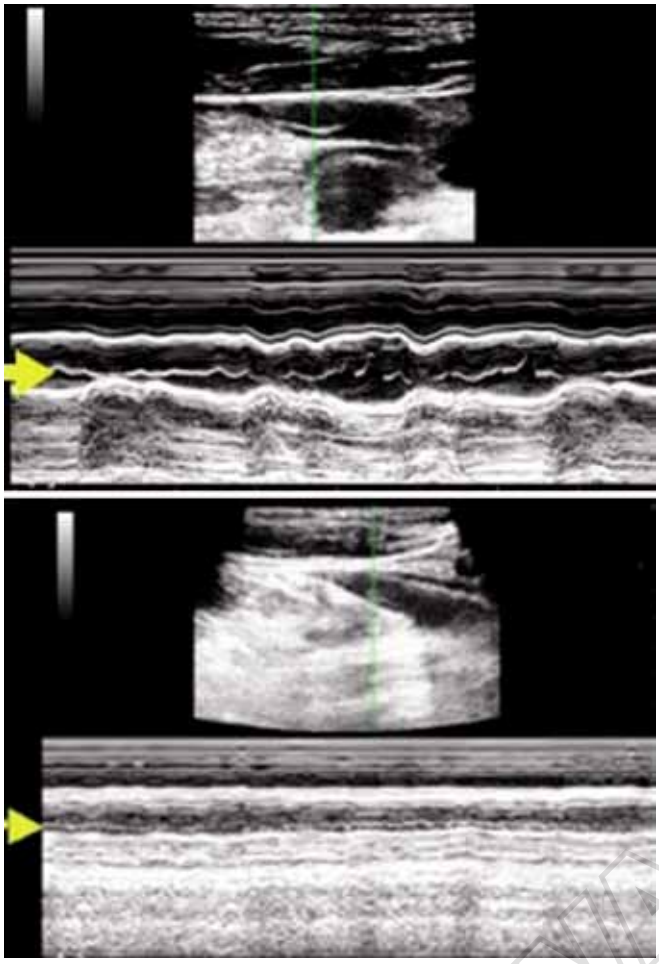

Figure 5.—M-mode evaluation of jugular valve.

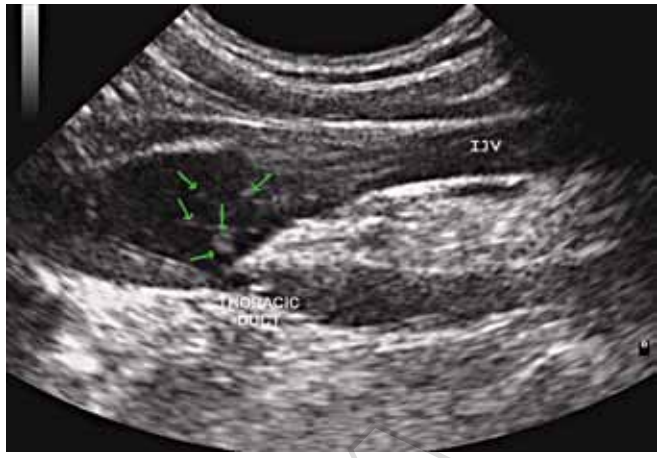

Figure 6.—Anomaly artefact.

tion of the IJVs (J1) have been found in 93% of post-mortem studies and in 87% of normal individuals.[54] Valves were not present in other segments. When a valve is detected it should be evaluated both in the transverse and longitudinal planes. The cusps of a normal valve should be oriented/angled in the direction of the blood flow and they should move freely with respect to the respiration phases. When the leaflets are open they should be parallel and close to the jugular wall.

The major anomalies which can be found at the level of the IJV valve are: flap, septum, annulus, immobile leaflets, immobility limited to one of the two leaflets, double channels, anomalous orientation of the valve leaflets (*e.g.*, inverted position of the leaflets, leaflets positioned on the lateral side of the jugular wall).[1-9, 46] Similarly to cardiac valve evaluation by echo-cardiography and/or in the deep venous system of the lower extremity,[55, 56] mobility of the valve cusps can be further documented by using the M-mode function, as shown in Figure 5.

Artifacts on B-mode

Two major artifacts can be found during the B-Mode examination of the IJV. They are believed to be produced by the lymph and the vagus nerve. The thoracic duct, especially after food intake, creates streams of lymph which are seen as hyper-echoic filaments within the vessel lumen (Figure 6). These filaments should not be mistaken for venous valve cusps because they do not have the periodically repeated movements typical of a valve cusp.

The vagus nerve is located posterior to the IJV, but on B-mode imaging it may produce an artifact in the middle of the IJV. The vagus nerve may appear as parallel linear echoes within the IJV, which can be misinterpreted as an intraluminal defect (Figure 7A). This artifact may be avoided by angling the probe away from the vagus nerve. Alternatively, this artifact can be proven by positioning the probe in the longitudinal position, where the nerve is visible on ultrasound because of longitudinal hyper-echoic thickening of the neural guaina and fibers In Figure 7A, B the echoes emitted by the transducer reflect a false image of the vagus nerve appearing inside the IJV.

Another artifact is the mirror artifact, a reflection given by the high acoustic reflection of the front wall of the vein. When the sound beam hits a strong interface (such as the an-

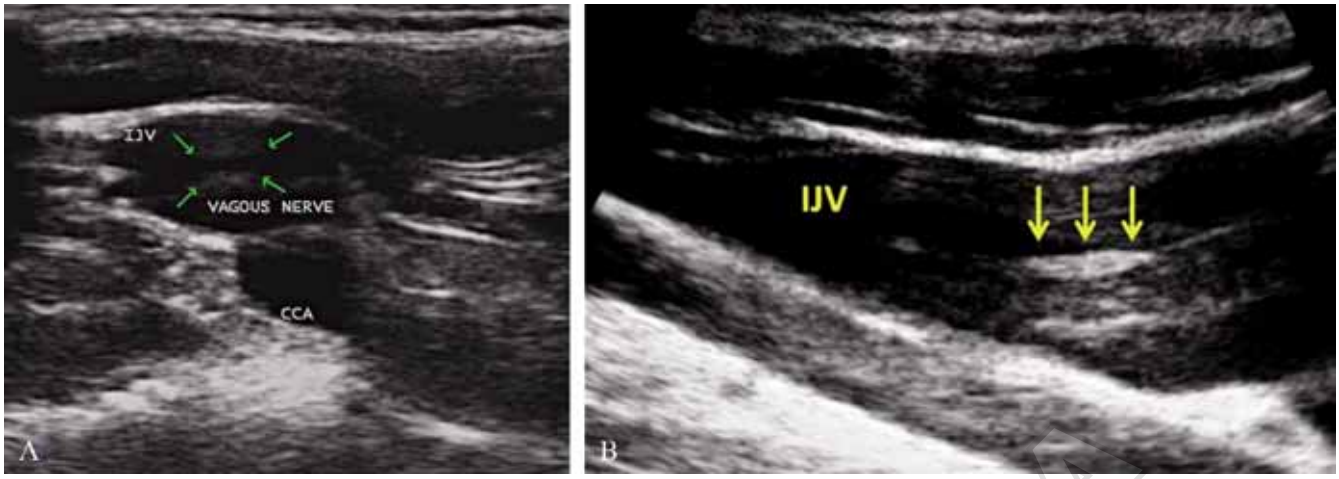

Figure 7.—B-mode artifact.

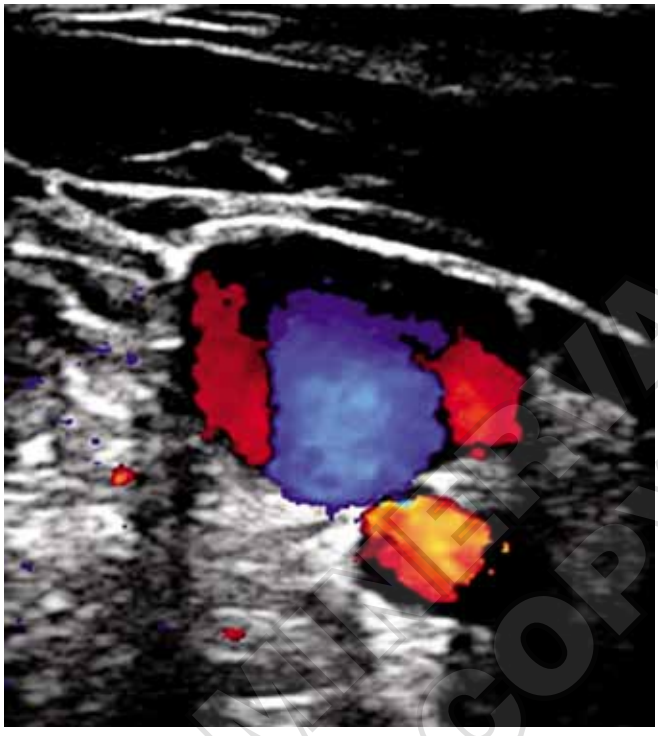
Figure 8.—Bidirectional flow in the IJV.

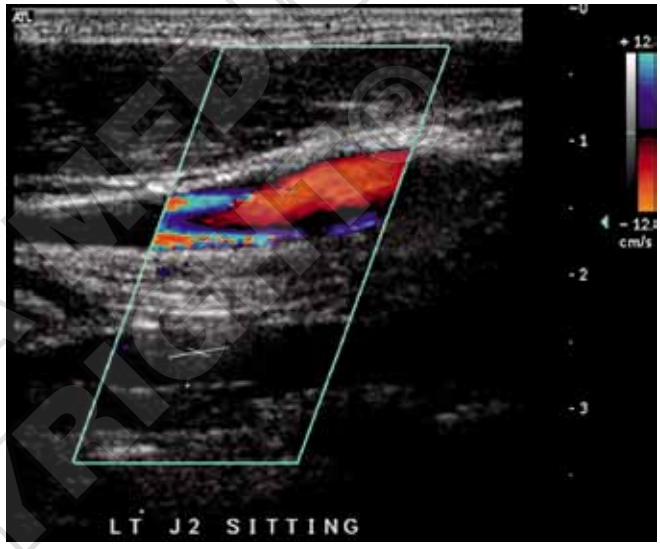

Figure 9.—Bidirectional flow in the IJV.

terior wall of IJV), at an angle other than 90°, that beam is rerouted. This change in the sound beam course takes longer to return to the machine, which results in the object appearing deeper than it truly is. In the figure, some of the echoes emitted by the transducer reflect a false images of the anterior wall of vein appearing as an intra luminal structure (Figure 7B).

Hemodynamic evaluation

Hemodynamic evaluation starts from the lower end of the middle segment of the IJV (J2) which is imaged in transverse view in the color mode. It is better to follow the IJV upwards to J3, observing the flow direction by means of color mode, asking the patient to breath quietly through the nose. Any irregularities that may appear (absence of flow, turbulences, reflux) in the color mode (Figure 8) will require verification by longitudinal imaging (Figure 9) in order to study the flow direction and duration of reflux/bidirectional flow by means of Doppler spectral analysis recordings (Figure 10) and/

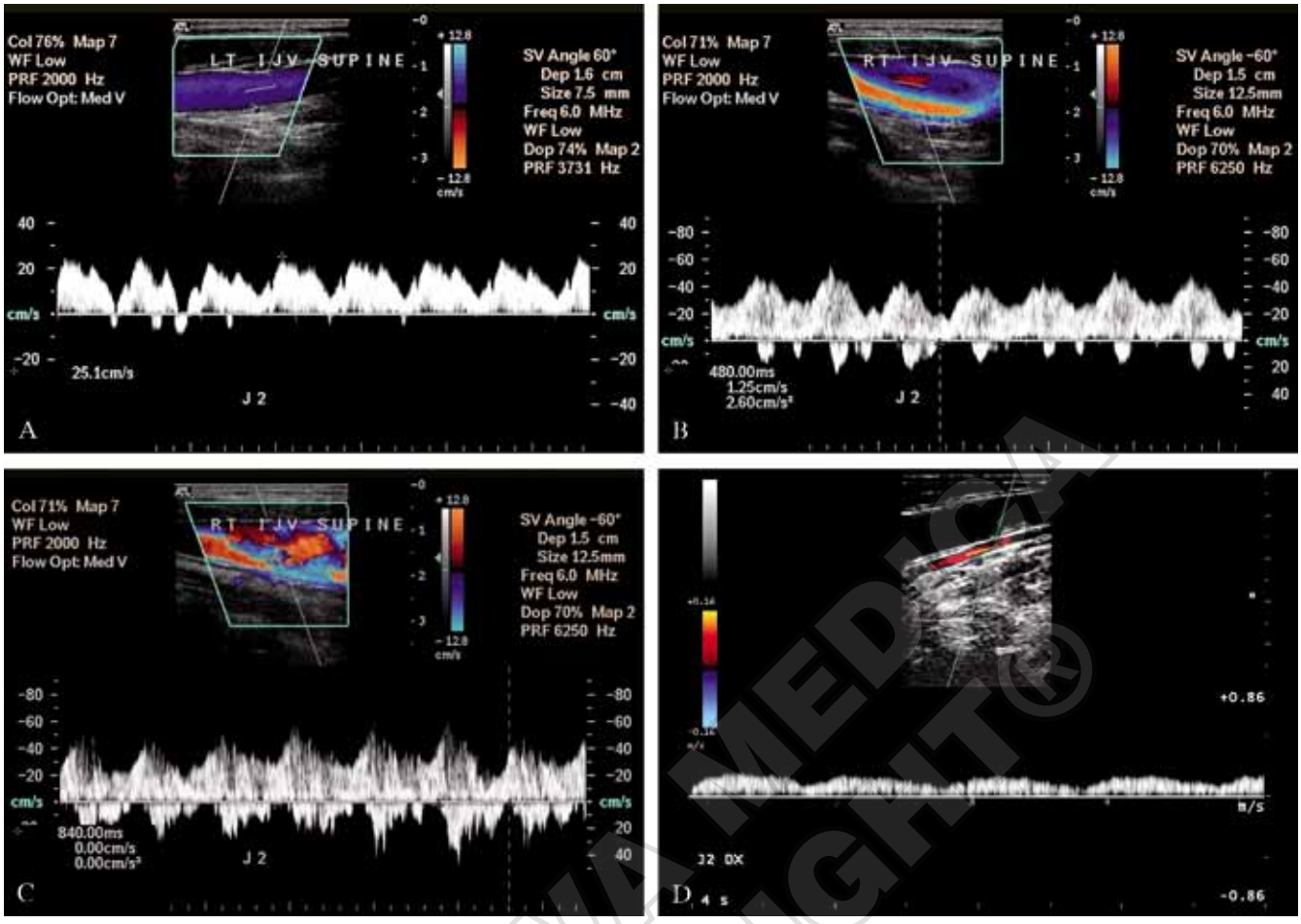

Figure 10.—Duration of reflux and flow direction.

or spectral analysis using multi-angle Doppler (Figure 11).

In the longitudinal plane, careful attention should be paid to the steering of the color flow box, ensuring an angle in relation to the vessel (Figures 9, 10). Although the >0.5 and >0.88 s has been suggested as the cut-off value for reflux through the jugular valve [57] this value was originally recorded under Valsalva at J1. In contrast, reflux associated with CCSVI is elicited by the activation of the thoracic pump and, sometimes, may last for several seconds (Figure 10).[1, 58] Reflux or absence of flow may occur and can be detected in any segment of IJV. Flow recording of both abnormalities is particularly significant at the end of the expiratory phase; flow evaluation does not require Valsalva at all. Recording of flow abnormalities should be made with opening of the Doppler sample gate wide (Figure 10). We suggest to insonate the lower part of the IJV (J1) last, after careful evaluation of the J2 and J3 segments.

At J1 level, turbulence and short time reflux (<0.88 s) should be considered normal because they are the physiological expression of flow close to valve cusps. This reflux is usually confined around the leaflets, and can be increased by respiration. If this reflux can be seen also in the IJV above the origin of the widening (bulb), this has to be considered as pathological reflux (Figure 9). The optimum cut off point for duration of reflux is under review and needs to be established; duration >0.5 s and >0.88 s are currently the most used values. The >0.88 s value for IJV reflux/bidirectional flow has been defined and used in prior studies for Criterion 1. It is recommended that recordings are made as shown in Figure 10, with measurements of duration of reflux in prospective observational studies in which patients undergo venography, so that the

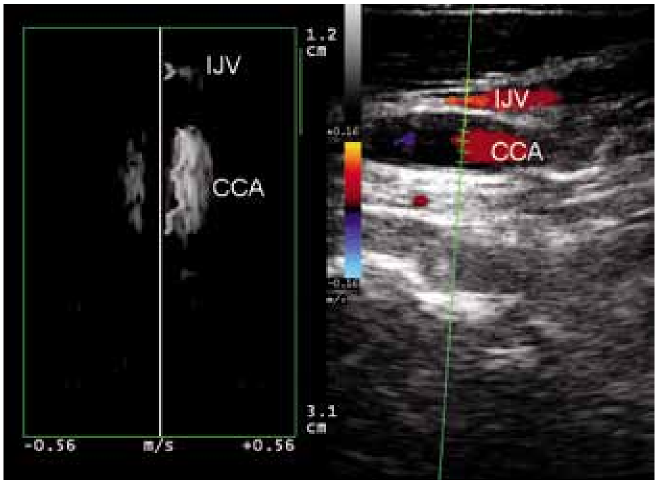

Figure 11.—Long lasting reflux.

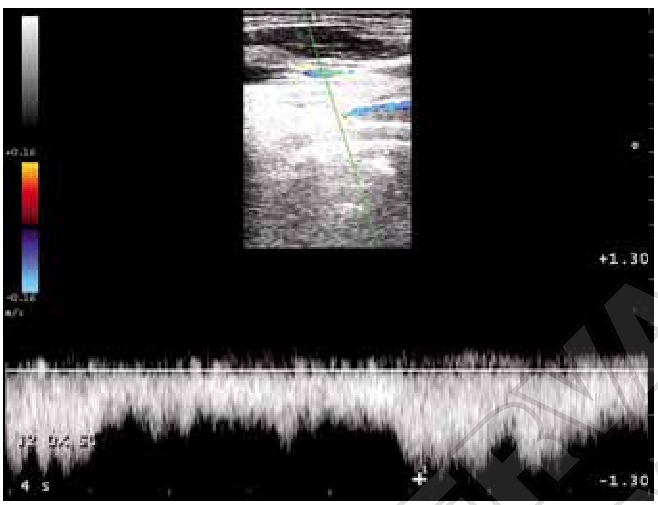

Figure 12.—Example of increased flow velocity.

optimum cut off point for duration of reflux associated with CCSVI can be determined.

The normal Doppler blood velocity in the IJV (lying or sitting) has been quoted as <70 cm/s.[10] A very high velocity in one IJV (Figure 12) can point towards a stenotic lesion, indicating a need to carefully assess for stenotic lesion, if not identified at the initial B-mode evaluation. Although this is not a criterion for CCSVI, it can be a helpful tool. Further research is required and more data to determine optimum velocity cut-off points. For this reason, it is recommended that in prospective observational studies which include normal individuals and patients with MS, velocities are measured in all segments of IJV (see perspectives in Appendix 5).

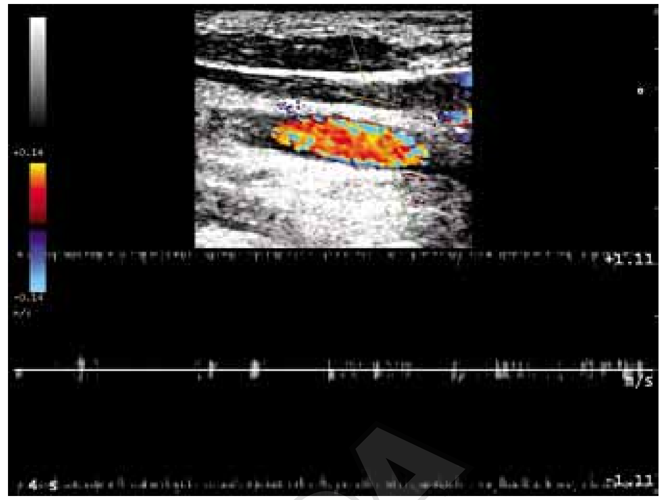

Figure 13.—Example of absence of detectable flow.

In a large number of cases, no flow can be detected within the IJV, which may suggest the presence of severe obstruction. There are two main possibilities: 1) the flow is not detected because the IJV is almost completely collapsed and cannot be distended by a Valsalva maneuver; this is compatible with a hypoplastic IJV; 2) the flow is not detected (velocity too low to be detected even at very low PRF) but the lumen of the IJV is clearly visible. Absence of flow in color Doppler mode should be confirmed by Doppler spectral analysis and absence of thrombosis by compression (Figure 13). This is compatible with absent flow in a filled IJV. Sometimes, especially when the Doppler sample is placed above the septum/immobile cusps the spectrum may show very low velocities related to little intraluminal movements and velocity cannot be increased by thoracic pump activation.

An IJV blood flow "block" (despite deep inspirations) has to be considered as a CCSVI criterion if no flow can be detected within an IJV both in the supine and sitting position. Alternatively, reflux within a jugular is considered a positive criterion if coupled with absence of flow in the other posture, or *vice versa*.

Stenosis in the lower IJV may activate collateral circulation. Collateral circulation may be observed at the levels of junction of the IJV with the anterior branch of the retromandibular vein, the common facial vein and the lingual vein, or commonly, at the level of the superior thyroid vein (Figure 14).

Absence of flow in the upper IJV may also activate collateral circulation. Flow may be noted in the lower IJV segment from the superior and mid thyroid vein collaterals draining into the lower IJV, or deep cervical vein draining into the lower IJV.

Measurements of cross-sectional area (CSA)

Perform the CSA measurements in transverse B-mode scans of the middle segment (J2) using the appropriate ellipsoid area measuring tool and/or auto area especially when in the vein is collapsed (Figure 15). Measurement can be performed with or without activation of the color mode. If color mode is used, the color gain should be adjusted so that the color does not obscure the vessel wall.

The measurement has to be performed at the same point, in both supine and sitting positions. Measurement of CSA has to be obtained initially in supine position, and then in sitting position. The IJV mid (J2) section can be identified through the relationship with the thyroid gland or by marking the measurement point on the skin. The transducer has to be kept almost perpendicular to the patient's neck in order to produce a "perfect" transverse section of the IJV (a certain inclination with respect to the 90° is still needed in order to be able to get a sufficient Color Doppler signal). The perfect circular shape of the common carotid artery can be used as a reference for the correct positioning.

How to perform CCSVI examination of vertebral veins (VV)

Evaluate vertebral veins with the transducer positioned longitudinally. When the patient is in the supine position, the blood flow within the VV is slower and a lower color doppler PRF and wall filter is needed (with respect to the IJV Color Doppler examination). The B-mode visualization of the VV is not easy and therefore a color-Doppler examination should be used from the beginning. VV have to be examined in visible segments (the easiest segment to be examined is between C5 and C6) (Figure 16).

Reflux within the VV is usually activated during the expiratory phase of the respiratory cycle. Reflux within the VV is represented by a complete reversal of blood flow direction lasting more than one second. A Doppler spectral waveform should be recorded. A continous reversed flow may be seen sometimes (opposite to the direction of physiological flow). This reversed flow, which is also considered as abnormal (reflux), may be the result of activation of collaterals connecting extravertebral with intravertebral veins.

Reflux within the VV has to be considered as a positive CCSVI criterion if it is present in the same VV both in the supine and sitting positions. Alternatively, a positive criterion can be assigned if reflux in one position is associated with absence of flow in the other position.

A VV blood flow "block" (despite deep inspirations and low PRF) (Figure 17) has to be considered as a positive CCSVI criterion if no flow can be detected within a VV both in the supine and sitting positions. VV reflux and/or "block" have to be assessed in the same segment at the end of the respiratory phase.

CCSVI examination of the intracranial veins

Transcranial investigation of the parenchymal veins and dural sinuses can be performed through well established transtemporal and transoccipital approaches.[59-61] The presence of reflux in the petrosal sinuses detected through the supracondylar window has been proposed as a criterion that can be used to diagnose CCSVI. Because insonation of the petrosal sinuses can be achieved with the Doppler angle close to 90°, detection of reflux in the form of bidirectional flow can be made only using a multi-angle Doppler system, such as the Quality Doppler Processing technology (QDP). QDP enables the operator to understand which is the blood flow direction within the examined cerebral veins: a proper adjustment of the PRF is necessary in order to clearly visualize the direction without background Doppler noise (Figure 18).[15, 58, 59]

As CCSVI is an extracranial venous pathology, because QDP technology is not available on all ultrasonic scanning systems, and as more data are needed to determine the contribution of intracerebral reflux to the final diagnosis of CCSVI, it is not currently recommended as

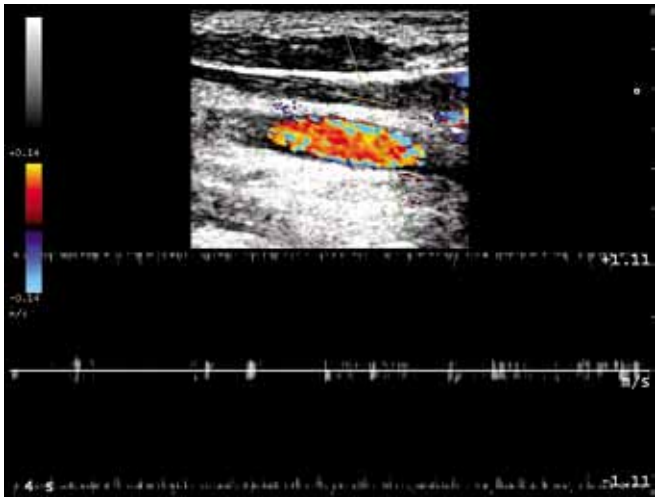

Figure 14.—Shunt into the thyroid vein.

part of the routine procedure. For details see Appendix 6.

Ultrasonographic criteria for CCSVI

Introduction

Five criteria for CCSVI were previously described [1-16] for the recommended diagnosis of CCSVI. Table II compares the published criteria with the criteria recommended by the Faculty in 2011.

All measurements should be performed on both sides, and in both, the sitting and lying positions. Criteria 1 and 4 are positive only if present in both positions.

The above criteria have been developed empirically (Table II), based on physiology of cerebral venous return, so that the presence of two or more of these would ensure a very high sensitivity. The Faculty recommends also to use duplex examination criteria for post-operative surveillance (Appendix 7).

The prevalence of each one of these criteria in patients with MS and healthy controls based on eight published series are summarised in Table III. It appears that criterion 3, concerning the detection of stenoses and/or intraluminal defects such as septa and fixed valve leaflets, had the highest prevalence (67% of MS patients and 18% in healthy controls). Criterion 1, on the presence of reflux in the IJV in both postures and/or the

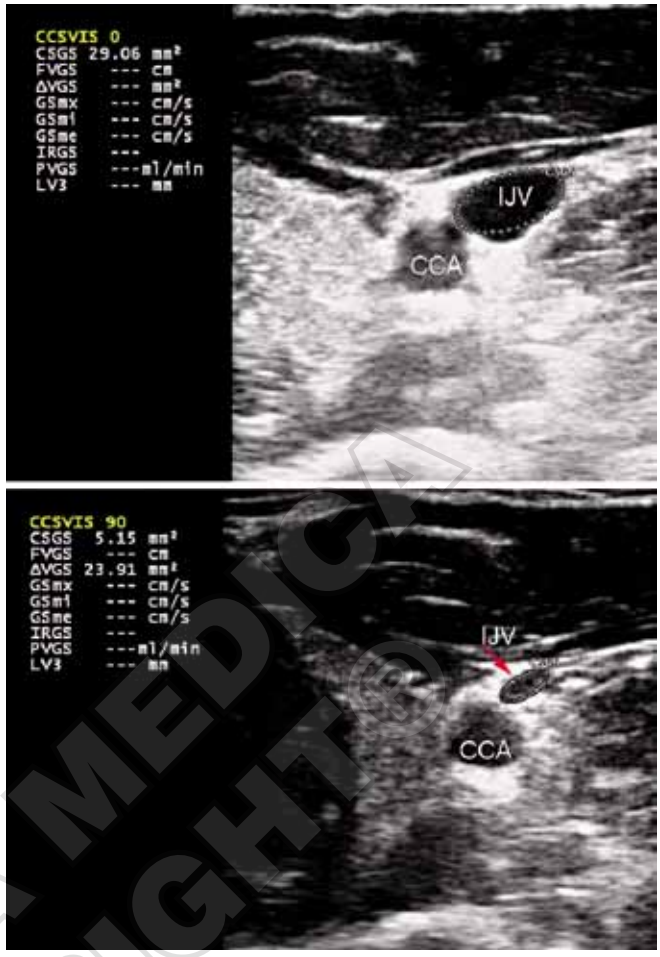

Figure 15.—Example of cross sectional area (CSA) measurement of the IJV.

presence of reflux in one posture and absence of flow in the other, was the second most prevalent criterion (60% of MS patients *vs*. 9% of healthy controls). The prevalence of criteria 2, 4 and 5 was much lower, 36%, 26% and 31%, respectively. The presence of two or more criteria was found in 73% of patients with MS and in 8.5% of controls.

Four data bases are available (Bastianello and Zamboni databases released at the Conference), plus publications from Mayer [11] and Doepp [10] that can be used to analyze the prevalence of all the possible combinations of two or more criteria present (Table IV). It can be seen that two criteria were present in 209 (23.3%) of the 895 patients, with 1+3 being the commonest combination followed by 1+5 and 3+4. Three or more criteria were present in 487 (54.3%) of the 897 patients.

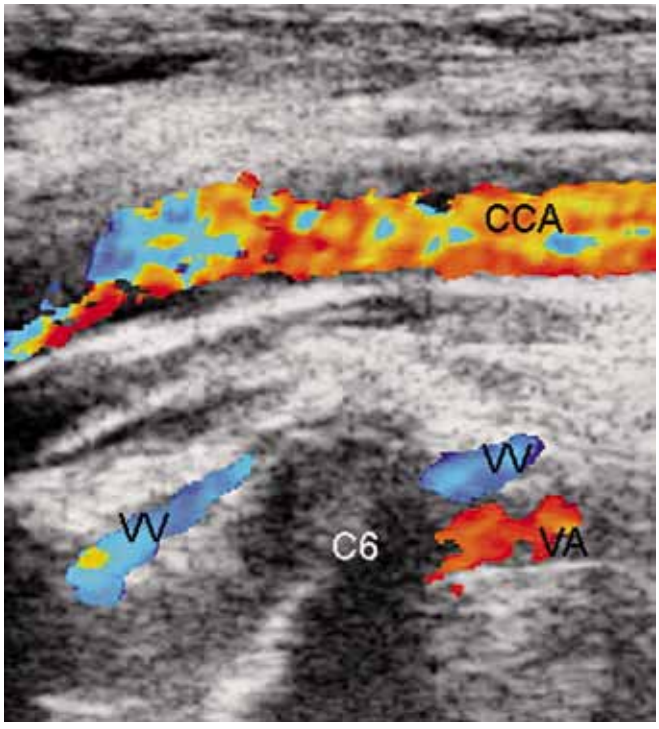

Figure 16.—Example of color-Doppler vertebral vein assessment.

So far only three publications have compared ultrasound findings with venographic findings (Table I). In the presence of two or more criteria, the Ferrara group, and the Ferrara-Buffalo group [1, 3] have found a 100% sensitivity; to the contrary, venography in 7 patients with suspected MS and positive CCSVI criteria performed by Baracchini *et al*.[13] showed no stenotic or obstructive lesions. Small numbers and variability in the way ultrasound examination has been performed may explain this discrepancy. Routine venography in 49 patients with MS without prior ultrasound examination performed by the team at the American University of Beirut has found stenotic lesions in 7 (24%) of 29 patients with early MS and 12 (92%) of 13 patients with late MS.[12]

The available data do not allow the determination of the value of screening with ultrasound in terms of sensitivity, specificity, PPV, NPV and overall accuracy against the goldstandard: venography. In particular, we do not know how many patients with CCSVI lesions are missed in the absence of any ultrasonic criteria or only one.

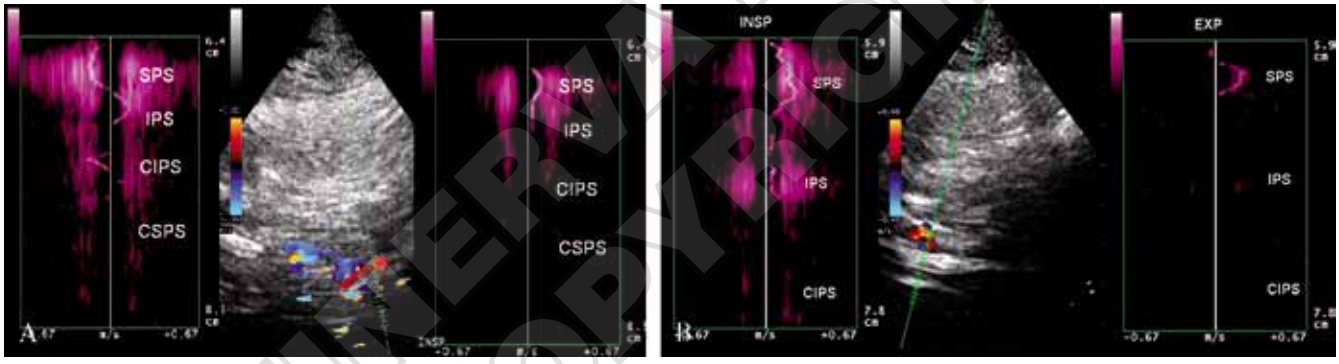

Figure 17.—Example of "blocked" VV.

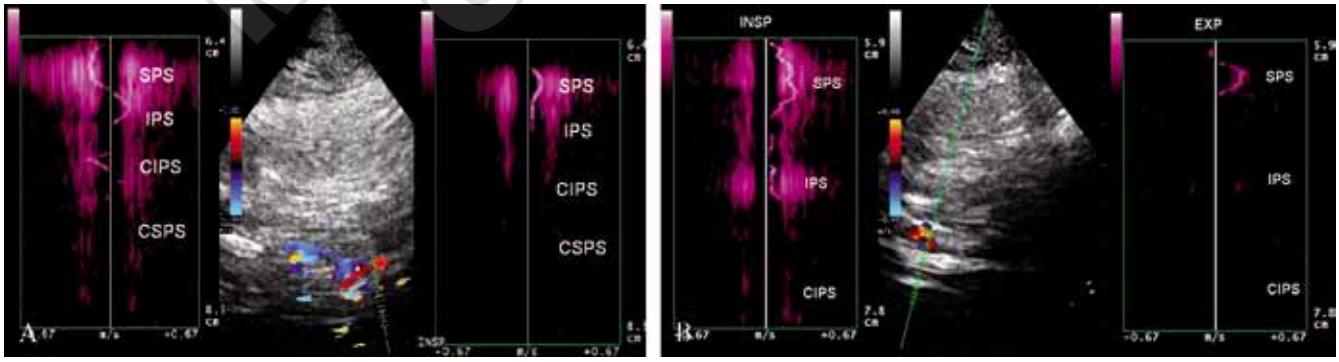

Figure 18.—Intracranial reflux detected by multiangle Doppler.

TABLE II.—*The prevalence of each one of the criteria in patients with MS and healthy controls (HC) based on eight published series*

CRITERIA	Reference	MS N = 1329	**HC** N = 455	Total MS	Total HC	OR (95% CI), P*
1. Reflux in the IJV and/or in the VV in supine and up-right posture OR Reflux in one of the two postures and absence of flow in the other.	Zamboni (38)	76/109	0/177	798/1329 60%	40/455 9%	15.6 (11-22), < 0.0001
	Al-Omari (5)	18/25	7/25			
	Simka (6)	31/70	np			
	Zivadinov (4)	130/289	33/163			
	Doepp (8)	0/56	0/20			
	Baracchini (11)	12/50	0/50			
	Mayer (9)	0/20	0/20			
	Bastianello (7)	531/710	np			
2. Reflux in the intracranial veins	Zamboni (38)	55/109	0/	478/1329 36%	15/455 3%	17.1 (10-29). < 0.0001
	Al-Omari (5)	np	np			
	Simka (6)	np	np			
	Zivadinov (4)	104/222	15/118			
	Doepp (8)	1/56	0/20			
	Baracchini (11)	0/50	0/50			
	Mayer (9)	0/20	0/20			
	Bastianello (7)	318/710	np			
3. High resolution B-mode evidence of proximal IJV stenoses and/or intraluminal defect	Zamboni (38)	30/109	1/177	889/1329 67%	80/455 17.5%	9.5 (7-12) < 0.0001
	Al-Omari (5)	23/25	0/25			
	Simka (6)	61/70	np			
	Zivadinov (4)	185/289	63/163			
	Doepp (8)	0/56	0/20			
	Baracchini (11)	8/50	0/50			
	Mayer (9)	13/20	16/20			
	Bastianello (7)	569/710	np			
4. Flow not Doppler detectable in the IJV and/or VV in supine and up-right posture.	Zamboni (38)	35/109	1/177	351/1329 26%	16/455 3.5%	9.8 (6-16), < 0.0001
	Al-Omari (5)	0/25	0/25			
	Simka (6)	37/70	np			
	Zivadinov (4)	30/289	12/163			
	Doepp (8)	5/56	1/20			
	Baracchini (11)	3/50	1/50			
	Mayer (9)	0/20	1/20			
	Bastianello (7)	241/710	np			
5. CSA of the IJV in up-right > CSA supine	Zamboni (38)	61/109	21/177	408/1329 31%	65/455 14%	2.7 (2-4). < 0.0001
	Al-Omari (5)	4/25	0/25			
	Simka (6)	28/70	np			
	Zivadinov (4)	33/289	11/163			
	Doepp (8)	4/56	3/20			
	Baracchini (11)	8/50	3/50			
	Mayer (9)	0/20	0/20			
	Bastianello (7)	270/710	np			
≥2 Positive criteria	Zamboni (38)	109/109	0/177	974/1329 73%	39/455 8.5%	29 (20-41), < 0.0001
	Al-Omari (5)	21/25	0/25			
	Simka (6)	63/70	np			
	Zivadinov (4)	162/289	37/163			
	Doepp (8)	0/56	0/20			
	Baracchini (11)	8/50	1/50			
	Mayer (9)	0/20	1/20			
	Bastianello (7)	611/710	np			

*The significance was tested with Fisher' two sided exact test followed by Odds ratio assuming, as reported by the Authors, that sonographic technique is the same between studies. The use of data pooling to derive Odds Ratios relatively underestimates the effect of small negative studies.

The high prevalence of CCSVI lesions in patients with MS justifies performance of both ultrasound and venography in an adequate series of patients blindly. Ultrasound should be performed by a team that has been through their learning curve and venography should not be withheld in patients with normal ultrasound findings. Patients admitted to such a study should not be preselected by a previous positive ultrasound test. Such a study will provide information not only on sensitivity, specificity, PPV, NPV and overall accuracy, but also on the contribution of individual criteria and their association with different type of lesions.

Pending the availability of such data the Faculty suggests that the presence of any two of the reversed criteria [1, 3-5] described below in detail, indicate CCSVI.

Criterion 1: Reflux in the IJV and/or VV

a) Bidirectional flow in one or both of the IJVs in both postures or bidirectional flow in one position with absence of flow in the other position (see criterion 3). These findings suggest IJV stenosis;

b) reversal or bidirectional flow in one or both of VVs in both positions. These findings suggest stenosis in the azygos vein, based on reports controlling the Doppler parameter in comparison with catheter venography.[1, 3]

Criterion 3: IJV stenosis

a) Severe reduction of the CSA of IJV in the supine position <0.3 cm^2 which does not increase with Valsalva manoeuvre (performed at the end of the examination);

b) intraluminal defects such as webs, septa or malformed valves combined with hemodynamic changes (increased velocity, absence of flow, reflux/bidirectional flow, etc). M-mode investigation of leaflets may clarify if they are mobile or not.

Criterion 4: absence of detectable flow in the IJV and/or VV

Outflow obstruction in the cervical veins indicated by:

a) absence of Doppler signal in the IJV and/or the VV, even after deep inspiration, in both sitting and supine positions or

TABLE III.—*The prevalence of combinations of 2 or more criteria present in MS patients (From Bastianello and Zamboni databases and publications from Mayer [9] and Doepp [8]*

Criteria and their combination	MS Patients N = 895	%
1+2	19/895	2.1
1+3	81/895	9
1+4	13/895	1.4
1+5	21/895	2.3
2+3	27/895	3
2+4	9/895	1
2+5	8/895	0.9
3+4	20/895	2.2
3+5	4/895	0.4
4+5	7/895	0.7
1+2+3	110/895	12.3
1+2+4	9/895	1
1+2+5	22/895	2.4
1+3+4	42/895	4.7
1+3+5	83/895	9.3
1+4+5	7/895	0.7
2+3+4	7/895	0.7
2+3+5	4/895	0.4
2+4+5	6/895	0.6
3+4+5	11/895	1.2
1+2+3+4	33/895	3.6
1+2+3+5	44/895	4.9
1+3+4+5	61/895	6.8
1+2+4+5	8/895	0.9
2+3+4+5	6/895	0.6
1+2+3+4+5	34/895	3.8

b) in one posture but with bidirectional flow detected in the other position. These findings are associated with stenosis proximal to the point of assessment.

Criterion 5. Abnormal change of the IJV CSA with change in position (change in hydrostatic pressure)

A CSA of the IJV which (a) is greater in the sitting position than in the lying position or (b) appears almost unchanged despite change in posture.

All measurements should be performed on both sides, and in both positions. Remember that reflux/bidirectional flow and absence of flow become diagnostic criteria only when demonstrated in the same cervical venous segment in both postures. However, absence of flow in one position (*e.g.*, sitting) in the presence of reflux in the other position can be considered a positive criterion, provided they occur in the

same vein. The presence of reflux or absence of flow in a single location in the same venous segment in only one position is not in itself a positive criterion. However, it weighs in the score if calculation of the venous hemodynamic insufficiency severity score (VHISS) is contemplated (see Appendix 4).

Criterion 2: bidirectional flow (or reflux) in the intracranial veins and sinuses.

This is potentially an additional criterion (see Appendix 6 for methodology).

Because not all the authors have used the same transcranial approach and because the QDP system is not available on all the equipment the contribution of intracranial reflux is currently under debate. For these reasons and pending more data, the routine use of this criterion is not currently recommended.

Based on the available evidence (Table IV) omission of criterion 2 in patients with three or more criteria will still result in a positive diagnosis for CCSVI. Omission of criterion 2 in the patients with only two positive criteria will result in 63 (7%) of the 895 patients being characterised as having a negative finding.[1, 8] Thus, if the QDP system is available, scanning the intracranial veins and using criterion 2 is a logical option when only one of the other criteria is present.

CCSVI ultrasonographic screening in clinically isolated syndrome and in suspected early MS

A promising application of ultrasound CCSVI screening is the investigation of patients with the clinically isolated syndrome (CIS) or probable suspected MS. CIS is a first demyelization episode followed in about 50% of cases by recovery. In contrast, half of the patients progress toward clinically defined MS. No way to predict the outcome of CIS is currently available. The prevalence of CCSVI in CIS was found to be 38%.[4] Longitudinal evaluation is required to understand if CCSVI positive patients should have more chances to progress toward MS. In another study, in CIS and in early suspected MS the prevalence of CCSVI was found to be 16% *vs*. 2% in controls.[13] The presence of CCSVI increases the susceptibility to early MS of more than 9 folds.[63]

References

1. Zamboni P, Galeotti R, Menegatti E, Malagoni AM, Tacconi G, Dall'Ara S *et al*. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 2009;80:392-9.
2. Zamboni P, Consorti G, Galeotti R, Gianesini S, Menegatti E, Tacconi G *et al*. Venous collateral circulation of the extracranial cerebrospinal outflow routes. Curr Neurovasc Res 2009;6:204-12.
3. Zivadinov R, Galeotti R, Hojnacki D, Menegatti E, Dwyer MG, Schirda C *et al*. Value of MR venography for detection of internal jugular vein anomalies in multiple sclerosis: a pilot longitudinal study. Am J Neurorad 2011;32:938-46.
4. Zivadinov R, Marr K, Cutter G, Ramanathan M, Benedict RH, Kennedy C *et al*. Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS. Neurology 2011;77:138-44.
5. Al-Omari MH, Rousan LA. Internal jugular vein morphology and hemodynamics in patients with multiple sclerosis. Int Angiol 2010;29:115-20.
6. Simka M, Kostecki J, Zaniewski M, Majewski E, Hartel M. Extracranial Doppler sonographic criteria of chronic cerebrospinal venous insuffitiency in the patients with multiple sclerosis. Int Angiol 2010;29:109-14.
7. Zamboni P, Menegatti E, Weinstock-Guttman B, Schirda C, Cox JL, Malagoni AM *et al*. CSF dynamics and brain volume in multiple sclerosis are associated with extracranial venous flow anomalies: a pilot study. Int Angiol 2010;29:140-8.
8. Bastianello S, Bergamaschi F, Viselner G *et al*. An international multicenter observatory on prevalence of CCSVI in MS. BMC Neurology 2011 [In press].
9. Zaharchuk G, Fischbein NJ, Rosenberg J, Herfkens RJ, Dake MD. Comparison of MR and Contrast Venography of the Cervical Venous System in Multiple Sclerosis. AJNR Am J Neuroradiol 2011 [Epub ahead of print].
10. Doepp F, Paul F, Valdueza JM, Schmierer K, Schreiber SJ. No cerebrocervical venous congestion in patients with multiple sclerosis. Ann Neurol 2010;68:173-83.
11. Mayer CA, Waltraud P, Matthias WL, Nedelmann M, Bechmann I, Steinmetz H. The perfect crime? CCSVI not leaving a trace in MS. J Neurol Neurosurg Psychiatry 2011;82:436-40.
12. Yamout B, Herlopian A, Issa Z, Habib RH, Fawaz A, Salame J *et al*. Extracranial venous stenosis is an unlikely cause of multiple sclerosis. Mult Scler 2010;16:1341-8.
13. Baracchini C, Perini P, Calabrese M, Causin F, Rinaldi F, Gallo P. No evidence of chronic cerebrospinal venous insufficiency at multiple sclerosis onset. Ann Neurol 2011;69:90-9.
14. Wattjes MP, van Oosten BW, de Graaf WL, Seewann A, Bot JC, van den Berg R *et al*. No association of abnormal cranial venous drainage with multiple sclerosis: a magnetic resonance venography and flow-quantification study. Neurol Neurosurg Psychiatry 2011;82:429-35.
15. Centonze D, Floris R, Stefanini M, Rossi S, Fabiano S, Castelli M *et al*. Proposed chronic cerebrospinal venous insufficiency criteria do not predict multiple sclerosis risk or severity. Ann Neurol 2011;70:52-9.
16. Marder E, Gupta P, Greenberg BM, Frohman EM, Awad AM, Bagert B, Steve O. No Cerebral or Cervical Venous Insufficiency in US Veterans With Multiple Sclerosis. Arch Neurol 2011 [Epub ahead of print].
17. Lee BB, Laredo J, Neville R. Embryological background of truncular venous malformation in the extracranial venous pathways as the cause of chronic cerebrospinal venous insufficiency. International Angiology 2010;29:95-108.

18. Lee BB, Bergan J, Gloviczki P, Laredo J, Loose DA, Mattassi R *et al*. Diagnosis and treatment of venous malformations - Consensus Document of the International Union of Phlebology (IUP)-2009. International Angiology 2009;28:434-51.
19. Lee BB, Laredo J, Lee TS, Huh S, Neville R. Terminology and classification of congenital vascular malformations. Phlebology 2007;22:249-52.
20. Uflacker R. Atlas of vascular anatomy. An angiographic approach. Philadelphia, PA: Lippincot, Williams and Wilkins Eds; 1997.
21. Hamoud S, Nitecky S, Engel A, Goldsher D, Hayek T. Hypoplasia of the inferior vena cava with azygous continuation presenting as recurrent leg deep vein thrombosis. Am J Med Sci 2000;319:414-6.
22. Gates J, Hartnell GG. Demonstration of inferior vena cava patency by retrograde azygous venography. Cardiovasc Intervent Radiol 1995;18:419-21.
23. Lane EJ, Heitzman ER, Dinn WM. The radiology of the superior intercostals veins. Radiology 1976;120:263-7.
24. Chasen MH, Charnsangavej C. Venous chest anatomy: clinical implications. Eur J Radiol 1998;27:2-14.
25. Mammen T, Keshava SN, Eapen CE, Raghuram L, Moses V, Gopi K *et al*. Transjugular liver biopsy: a retrospective analysis of 601 cases. J Vasc Interv Radiol 2008;19:351-8.
26. Dilenge D, Perey B, Geraud G, Nutik S. Angiographic demonstration of the cervical vertebral venous plexus in man. J Can Assoc Radiol 1975;26:77-81.
27. Zelli GP, Messinetti S, Condorelli S. Original technic of internal jugular phlebography by puncture of the external jugular vein with retrograde emmission of the contrast media. Prog Med 1964;15:681-8.
28. Gejrot T, Lauren T. Retrograde venography of the internal jugular veins and transverse sinuses; technique and roentgen anatomy. Acta Otolaryngol 1964;57:556-70.
29. Gejrot T. Retrograde jugulariography in the diagnosis of abnormalities of the superior bulb of the internal jugular vein. Acta Otolaryngol 1964;57:177-80.
30. Leriche H, Aubin ML, Aboulker J. Cavo-spinal phlebography in myelopathies. Stenoses of internal jugular and azygos veins, venous compressions and thromboses Acta Radiol Suppl 1976;347:415-7.
31. Tzuladze II. The selective phlebography of the large tributaries of the vena cava system in the diagnosis of venous circulatory disorders in the spinal complex. Zh Vopr Neirokhir Im N N Burdenko 1999;2:8-13.
32. Zamboni P, Galeotti R, Menegatti E, Malagoni AM, Gianesini S, Bartolomei I *et al*. A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency. J Vasc Surg 2009;50:1348-57.
33. Zamboni P, Galeotti R, Weinstock-Guttman B, Kennedy C, Salvi F, Zivadinov R. Venous angioplasty in patients with multiple sclerosis: results of a pilot study. Eur J Vasc Endovasc Surg 2011 [Epub ahead of print].
34. Malagoni AM, Galeotti R, Menegatti E, Manfredini F, Basaglia N, Salvi F *et al*. Is chronic fatigue the symptom of venous insufficiency associated with multiple sclerosis? A longitudinal pilot study. Int Angiol 2010;29:176-82.
35. Ludyga T, Kazibudzki M, Simka M, Hartel M, Swierad M, Piegza J *et al*. Endovascular treatment for chronic cerebrospinal venous insufficiency: is the procedure safe? Phlebology 2010;25:286-95.
36. Petrov I, Grozdinski L, Kaninski G, Iliev N, Iloska M, Radev A. Safety profile of endovascular treatment for chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. J Endovasc Ther 2011;18:314-23.
37. Menegatti E, Genova V, Tessari M, Malagoni AM, Bartolomei I, Zuolo M *et al*. The reproducibility of colour Doppler in chronic cerebrospinal venous insufficiency associated with multiple sclerosis. Int Angiol 2010;29:121-6.
38. Schaller B. Physiology of cerebral venous blood flow: from experimental data in animals to normal function in humans. Brain Res Rev 2004;46:243-60.
39. Singh AV, Zamboni P. Anomalous venous blood flow and iron deposition in multiple sclerosis. J Cereb Blood Flow Metab 2009;29:1867-78.
40. Menegatti E, Zamboni P. Doppler haemodynamics of cerebral venous return. Curr Neurovasc Res 2008;5:260-5.
41. Gisolf, J, van Lieshout JJ, van Heusden K, Pott F, Stok WJ, Karemaker JM. Human cerebral venous outflow pathway depends on posture and central venous pressure. J Physiol 2004;560:317-27.
42. Valdueza, JM, von Munster T, Hoffman O, Schreiber S, Einhaupl KM. Postural dependency of the cerebral venous outflow. Lancet 2000;355:200-1Schreiber SJ, Lurtzing F, Gotze R, Doepp F, Klingebiel R, Valdueza JM. Extrajugular pathways of human cerebral venous blood drainage assessed by Duplex ultrasound. J Appl Physiol 2003;94:1802-5.
43. Doepp F, Schreiber SJ, von Münster T, Rademacher J, Klingebiel R, Valdueza JM. How does the blood leave the brain? A systematic ultrasound analysis of cerebral venous drainage patterns. Neuroradiology 2004;46:565-70.
44. Zamboni P, Menegatti E, Galeotti R, Malagoni AM, Tacconi G, Dall'Ara S, Bartolomei I, Salvi F. The value of cerebral Doppler venous haemodynamics in the assessment of multiple sclerosis. J Neurol Sci 2009;15:282:21-7.
45. Zamboni P. Regarding "No cerebrocervical venous congestion in patients with multiple sclerosis. Intraluminal jugular septation". Ann Neurol 2010;68:969.
46. Meyer-Schwickerath R, Haug C, Hacker A, Fink F, Seidel D, Hartung HP *et al*. Intracranial venous pressure is normal in patients with multiple sclerosis. Mult Scler 2011;17:637-8.
47. Beggs CB. Multiple sclerosis appears to be associated with cerebral venous abnormalities. Ann Neurol 2010;68:560-1.
48. Law M, Saindane AM, Ge Y, Babb JS, Johnson G, Mannon LJ *et al*. Microvascular abnormality in relapsing-remitting multiple sclerosis: perfusion MR imaging findings in normal-appearing white matter. Radiology 2004;231:645-52.
49. Zamboni P, Menegatti E, Weinstock-Guttman B, Dwyer MG, Schirda CV, Malagoni AM *et al*. Hypoperfusion of brain parenchyma is associated with the severity of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. BMC Medicine 2011;7:9-22.
50. Zamboni P, Menegatti E, Weinstock-Guttman B, Schirda C, Cox JL, Malagoni AM *et al*. The severity of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis is related to altered cerebrospinal fluid dynamics. Funct Neurol 2009;24:133-8.
51. D'Haeseleer M, Cambron M, Vanopdenbosch L, De Keyser J. Vascular aspects of multiple sclerosis. Lancet Neurol 2011;10:657-66.
52. Filippi M, Rocca MA. The multiple sclerosis mystery: is there a vascular component? Lancet Neurol 2011;10: 597-8.
53. Lepori D, Capasso P, Fournier D, Genton CY, Schnyder P. Highresolution ultrasound evaluation of internal jugular venous valves. Eur Radiol 1999;9:1222-6.
54. Kotani A, Hirano Y, Yasuda C, Ishikawa K. A new ultrasonographic technique for diagnosing deep venous insufficiency--imaging and functional evaluation of ve-

nous valves by ultrasonography with improved resolution. Int J Cardiovasc Imaging 2007;23:493-500.
55. Feigenbaum H. Role of M-mode technique in today's echocardiography. J Am Soc Echocardiogr 2010;23:240-57.
56. Nedelmann M, Eicke BM, Dieterich M. Functional and morphological criteria of internal jugular valve insufficiency as assessed by ultrasound. J Neuroimaging 2005;15:70-5.
57. Zamboni P, Galeotti R. The chronic cerebrospinal venous insufficiency syndrome. Phlebology 2010;25:269-79.
58. Baumgartner R W, Nirkko A C, Müri RM, Gönner F. Transoccipital Power-Based Color-Coded Duplex Sonography of Cerebral Sinuses and Veins. Stroke 1997;28:1319-23.
59. Stolz DE, Kaps M, Kern A, Babacan SS. Reference Data From 130 Volunteers Transcranial Color-Coded Duplex Sonography of Intracranial Veins and Sinuses. Stroke 1999;30:1070-5.
60. Walter U. Transcranial sonography-assisted stereotaxy and follow-up of deep brain implants in patients with movement disorders. Int Rev Neurobiol 2010;90: 274-85.
61. Zamboni P, Menegatti E, Viselner G, Bastianello S. Fusion imaging technology of the intracranial veins. Phlebology 2011 [In press].
62. Avruscio GP. Chronic cerebrospinal venous insufficiency and susceptibility to multiple sclerosis. Ann Neurol 2011 [Epub ahead of print].
63. Nicolaides AN and the Intersociety Scientific Committee; Investigation of Chronic Venous Insufficiency. A consensus statement. Circulation 2000;14:E126-63.

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APPENDIX 1
Clinical trials on CCSVI treatment

Clinical trials on CCSVI treatment currently available are the following:

1) A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency

— Status: published.[32]

This study evaluated the safety of CCSVI endovascular treatment and its influence on the clinical outcome of the associated MS. PTA of venous strictures in patients with CCSVI showed to be safe, and positively influenced clinical and QOL parameters of the associated MS compared to preoperative treatment. Restenosis rates were elevated in the IJV but promising in the AZY, suggesting the need to improve endovascular techniques.

2) Endovascular treatment for chronic cerebrospinal venous insufficiency (CCSVI)

— Status: published.[33]

This study confirmed the safety and suggests benefits for relapsing remitting MS patients. Currently it is the only study with control arm and blinded MRI measure. It has been demonstrated a trend to lower T2 lesion accumulation in treated patients along 6 months.

3) Multi-center registry for CCSVI Testing and Treatment

— ClinicalTrials.gov Identifier: NCT01205633

— Status: ongoing

— Patients suspected of CCSVI should register their participation in MRV testing, and if positive, for catheter venoplasty (with a catheter interventionist in their local community). The procedure should, but may not be covered by patients' insurance. Patients must be referred by their treating physician.

4) Study To Evaluate Treating Chronic Cerebrospinal Venous Insufficiency (CCSVI) in Multiple Sclerosis Patients

— ClinicalTrials.gov Identifier: NCT01089686

— Status: ongoing

— The purpose is to evaluate the safety, feasibility and efficacy of percutaneous transluminal angioplasty in treating extracranial venous obstructive lesions, and its influence on the clinical outcomes of MS patients that have been found to have CCSVI.

5) Evaluation of angioplasty in the treatment of chronic cerebrospinal venous insufficiency (CCSVI) in multiple sclerosis:

— ClinicalTrials.gov Identifier: NCT01201707

— Status: recruiting.

— The study is being done to determine if venous angioplasty is an effective treatment for CCSVI. The effectiveness of angioplasty in the treatment of CCSVI is being evaluated by comparison of two groups of patients: one group with CCSVI diagnosed on a venogram and treated with angioplasty, and one group with CCSVI diagnosed on a venogram but not treated.

6) Endovascular Treatment for Chronic Cerebrospinal Venous Insufficiency (CCSVI)

— ClinicalTrials.gov Identifier: NCT01264848

— Status: recruiting.

— This study is designed to evaluate Endovascular Correction of Chronic Cerebrospinal Venous Insufficiency (CCSVI) and Evaluation of Influence of These Treatments on the Symptoms of Multiple Sclerosis. Prospective open label cohort study

7) PREMiSe-Prospective Randomized Endovascular therapy in Multiple Sclerosis

— Status: ongoing (Buffalo, NY, USA)

— The aim of this study is to determine if endovascular intervention via balloon angioplasty to correct the blockages improves MS symptoms or progression.

8) BRAVE DREAMS - BRAin VEnous DRainage Exploited Against Multiple Sclerosis

— ClinicalTrials.gov Identifier: NCT01371760

— Status: not yet recruiting (Ferrara, Italy)

Aims of this study is to assess in a double blinded randomized control trial (RCT) study design safety and effectiveness of balloon angioplasty of the main extracranial and extravertebral veins in multiple sclerosis (MS) associated to chronic cerebrospinal venous insufficiency (CCSVI).

Mean follow-up one year. 10-20 Italian centers 445 relapsing remitting (RR)+ 234 secondary progressive (SP), overall 679 MS patients will be randomized, with expanded disability disease scale (EDSS) ranging 2-5.5, age 18-65.

APPENDIX 2

Screening for chronic cerebrospinal venous insufficiency (CCSVI: Report Form Proposal)

Name: ..... D.O.B.: ..... Date: ..... Subject No.: .....

Referring Dr: Dr. .....

REPORT

A. Supine

Right						Left					
	Flow Direction	PV cm/s	Reflux time(s)	Area cm^2	Valves, septa, etc.		Flow direction	PV cm/s	Reflux time(s)	Area cm^2	Valves, septa, etc.
J3				—		J3				—	
J2						J2					
J1				—		J1				—	
VV				—		VV				—	
Further Comments/Diagrams											

B. Sitting

Right						Left					
	Flow Direction	PV cm/s	Reflux time(s)	Area cm^2	Valves, septa, etc.		Flow direction	PV cm/s	Reflux time(s)	Area cm^2	Valves, septa, etc.
J3				—		J3				—	
J2						J2					
J1				—		J1				—	
VV				—		VV				—	
Further Comments/Diagrams											

Name: ..... D.O.B.: ..... Date: ..... Subject No.: .....

Referring Dr: Dr. .....

REPORT EXAMPLE

A. Supine

Right						Left					
	Flow Direction	PV cm/s	Reflux time(s)	Area cm^2	Valves, septa, etc.		Flow direction	PV cm/s	Reflux time(s)	Area cm^2	Valves, septa, etc.
J3	↓	59		—		J3	↓	56		—	
J2	↓↑	57	0.84			J2		55		0.66	
J1	↓↑	57	1.5	—	Fixed septum	J1	↓↑	47	1.5	—	Malaligned valve
VV	↓	32		—		VV	↓	20		—	
Further Comments/Diagrams											

B. Sitting

Right						Left					
	Flow Direction	PV cm/s	Reflux time(s)	Area cm^2	Valves, septa, etc.		Flow direction	PV cm/s	Reflux time(s)	Area cm^2	Valves, septa, etc.
J3	↓	32		—		J3	↓	40		—	
J2	↓	153		0.26		J2	↓	18		0.10	
J1	↓↑	32		—	Fixed septum	J1	↓↑	170		—	Malaligned valve
VV	↓	70		—		VV	↓	35		—	
Further Comments/Diagrams											

Additional investigation: intracranial veins

	Flow direction		Reflux >0.5 s	
Trans temporal approach Rosenthal vein	↑	↓↑	Y	N
Trans condylar approach Superior Petrosal Sinus Inferior Petrosal Sinus Controlateral Inferior Petrosal Sinus Controlateral Superior Petrosal Sinus Cavernous Sinus	↑	↓↑	Y	N

Example of final report and conclusion

Criteria	Description
1. Reflux IJV and\or VV in both postures Reflux in one posture and absence of flow in the other	Yes, No Segments: IJVr, IJVl, VVr,VVl
3. High resolution B-mode evidence of proximal IJV stenosies and/or other B-mode anomalies	Yes, No: Segments IJVr, IJVl CSA < 0.3: Segments IJVr, IJVl Flow velocity > 90 cm/sec: Segments IJVr, IJVl Fixed M-mode Evaluation: Segments IJVr, IJVl
4. Absence of flow IJV and\or VV in both postures	Yes, No Segments: IJVr, IJVl, VVr,VVl
5. CSA sitting > Supine in the IJV	Left Right
Additional criterion: 2. Reflux in the intracranial veins	Yes, No
Conclusions	CCSVI YES, CCSVI NO N. of fulfilled criteria…./ Affected segments: IJVr, IJVl, suspected AZY

Center: .....

Investigator: .....

Signature: .....

APPENDIX 3

Basic principles of fluid mechanics

This appendix has been written as a guide to those who intend to undertake research in this area and develop methods of measuring flow and/or pressure changes in the veins of the cerebrovascular circulation.

Very little physiological data exists regarding the pressure drop (pressure gradient) through the extracranial venous pathways from the brain to the heart. This is because veins are floppy vessels which change shape in response to postural and respiratory changes. Given the difficulties associated with taking physiological pressure measurements in extracranial veins, it is necessary to turn to theoretical calculations.

In any given vein the blood flow rate through the vessel, Q, is given by:

$$Q = \frac{P_{T1} - P_{T2}}{R} \quad (1)$$

Where, PT1 represents the total pressure of the blood entering the vessel, PT2 represents the total pressure of the blood leaving the vessel and R, represents the hydraulic resistance of the vessel. For any given point in the vein the total pressure, PT, is the sum of the static pressure, Ps, and the dynamic pressure, PD, and is given by:

$$P_T = P_S + P_D \quad (2)$$

The static pressure is given by:

$$P_S = \rho g h \quad (3)$$

The dynamic pressure is given by:

$$P_D = 0.5\rho v^2 \quad (4)$$

Where, ρ is the density of the blood, g is the acceleration due to gravity (i.e. 9.81 m/s^2, h is the head of fluid, and v is the velocity of the blood flow).

While it is difficult to accurately determine the pressure drop through veins, it is possible to determine an approximate value by applying Poiseuille's law:

$$\Delta P = \frac{v8L\mu}{r^2} \quad (5)$$

Where, L is the length of the vessel, m is the blood viscosity (i.e. 3.9 ´ 10^{-3} Pa.s), and r is the radius of the vein. From this it can be seen that the pressure drop through the vessel is inversely proportional to the square of the radius of that vessel. If the average velocity of the blood flow in a vein is known, then it is possible to determine an approximate value for the pressure drop across the vein, using equation 5.

While it is possible to calculate an approximate pressure drop using Poiseuille's law, the result obtained should be treated with caution. This is because Poiseuille's law applies strictly to straight tubes with no change in cross-sectional area. However, veins, being compliant vessels, readily change their cross-sectional area in response to changes in pressure. At any given point, as the static pressure increases, so the cross-sectional area of the vein will tend to increase. This will tend to reduce the blood velocity, with the result that the dynamic component of the total pressure will tend to reduce (see equation 2). Consequently, the pressure of the blood will be modified by the compliance of the vessel.

APPENDIX 4

The venous hemodynamic insufficiency severity score

The hemodynamic severity of CCSVI can be scored through the venous hemodynamic insufficiency severity score (VHISS), which was found to have a positive correlation with non-conventional MRI measurements, such as CSF flow dynamics, brain volume, cerebral blood flow, cerebral blood volume, and mean transit time.[7, 50, 51]

The VHISS is an ordinal measure of the overall extent and number of CCSVI criteria

with a higher value of VHISS indicating a greater severity of flow pattern anomalies. For each of the five CCSVI criteria a VHISS value can be assigned using the scheme described below. The minimum possible VHISS value is 0 and the maximum 16.

As regards criterion1 (reflux in the IJV and/or VV), there are four venous segments that can potentially exhibit reflux in each posture (supine or sitting). One point has been assigned for each segment with reflux in any posture. Consequently, criterion 1 has a VHISS contribution score that could range from a minimum of 0 to a maximum of eight.

The VHISS contribution score for criterion 2 (IJV stenosis) ranged from 0 to 2, depending on whether B-mode anomalies disturbing outflow were present in none, one or both of the IJVs, respectively. Criterion 2 is assigned a contribution score of 0 if either criterion 1 or criterion 3 should be positive for the presence, in either posture, of reflux or obstruction in the IJVof interest.

The scoring scheme for the contribution of criterion 3 (absence of flow in the IJV and/or VV) to the VHISS is the same as that for criterion 1 the difference being that only blocks are considered. No points are assigned for segments in which reflux in any posture has been detected under criterion 1.

Criterion 4 (change in CSA by changing posture:) has an overall VHISS contribution score between 0 and 4, calculated by assigning 0 to 2 points for each IJV. A CSA_{lying} greater than $CSA_{sitting}$ by 7 mm^2 or more is assigned 0. A CSA_{lying} greater than $CSA_{sitting}$ by less than 7 mm^2 is assigned 1. A CSA_{lying} which is less than $CSA_{sitting}$ is assigned 2. (The value of value 7 mm^2, corresponds to the 25^{th} percentile of DCSA distribution in healthy controls). Criterion 5 (reflux in intracranial veins) is assigned a VHISS contribution score of 1 if intracranial vein reflux was present in only one posture, and of 2 if it was present in both postures. The VHISS contribution score for this criterion was additionally weighted with a factor of 2 if reflux toward the subcortical gray matter could be detected. Consequently, the VHISS contribution score for criterion 2 could range from a minimum of 0 to a maximum of four.

The overall VHISS score was defined as a weighted sum of the scores contributed by each individual CCSVI criterion. The formula for VHISS calculations is:

$$\textbf{VHISS} = VHISS_1 + VHISS_2 + VHISS_3 + VHISS_4 + VHISS_5$$

The subscripts in this formula indicate the subscores for the five VH criteria.

APPENDIX 5

During the development of these guidelines the key question that was often asked was "What is the evidence". In the absence of evidence or limited evidence, the question became "What additional information is needed?". This process has revealed a number of key questions that require to be addressed by future studies. They are summarised in this appendix.

1. More studies are needed to determine the prevalence of different venous abnormalities in patients with MS, subgroups of MS and normal controls.
2. The range of velocities in different segments of the IJVs and in VVs in normal individuals without any lesions needs to be determined.
3. The range of velocities in different segments of the IJVs and in VVs in individuals with venographically established lesions needs to be determined.
4. The presence and duration of reflux (or bidirectional flow) in the IJVs of normal individuals and patients with stenotic or obstructive lesions needs to be determined.
5. In addition to criteria for the detection of CCSVI, criteria for the detection of individual venous lesions should be identified.
6. The methodology for volume flow measurements in the IJVs and VVs in supine and sitting positions and their reproducibility should be determined. Flow volume in normal individuals and patients with specific lesions of CCSVI should be studied.
7. The possible association between ultrasonic and venographic lesions with the pathology and symptoms of MS should be investigated.
8. The contribution of each of the proposed ultrasound criteria (1 to 5) and combinations of criteria in the detection of venographically established CCSVI needs to be determined.
9. The hemodynamics of the extracranial veins which behave like collapsible tubes need to be studied.
10. The value of comparing velocity between both sides in detecting a lesion on one side needs to be investigated. Another possible field of investigation is to correlate flow velocity with compensatory flow.
11. Doppler flow measurement in the extracranial veins, in up-right and supine position did not

demonstrate differences between MS patients and controls.[10] However, two studies [10, 42] published by the same group of investigators show a high variability and poor reproducibility of Doppler flow measurement in veins, previously recognized at a consensus conference on venous investigation.[64] However, by comparing normal controls to MS patients, it has been demonstrated that there is a much larger change in blood flow volume in normal subjects compared to MS patients when the subjects go from a supine to an upright position.[10, 46] These results need to be validated by further studies.

12. Changes in blood volume in the neck on moving the patient from supine to up-right should be investigated as a possible means of differentiating individuals with cervical vein outflow obstruction from those with normal veins.

APPENDIX 6

How to perform CCSVI examination of the intracranial veins

The classical transtemporal and more recently described transoccipital and frontal bone windows allow insonation of intracranial arteries and veins including deep cerebral veins (the Rosenthal vein, the Galen vein, and the internal cerebral vein) and the contralateral transverse sinus.[59-61] Figure 1 shows a well established plan of insonation of the midbrain. The midbrain appears as a butterfly-like structure in B-mode. The parenchymal vein more easily to detect is the Rosenthal vein, because of its anatomical relation with the posterior cerebral artery and midbrain. The blood is expected to flow away from the probe toward the Galen vein-straight sinus direction.

For the veins at the base of the brain (superior and inferior petrosal sinuses) a different transcranial approach by the means of fusion imaging technology with MRI has been demonstrated.[62] The

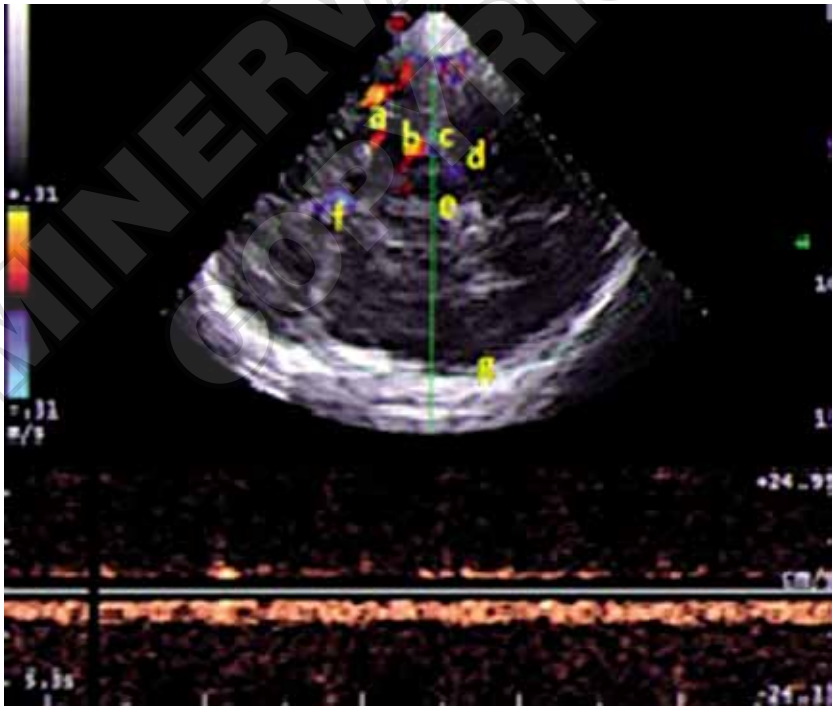

Figure 1.—Trans-temporal approach at the level of midbrain.

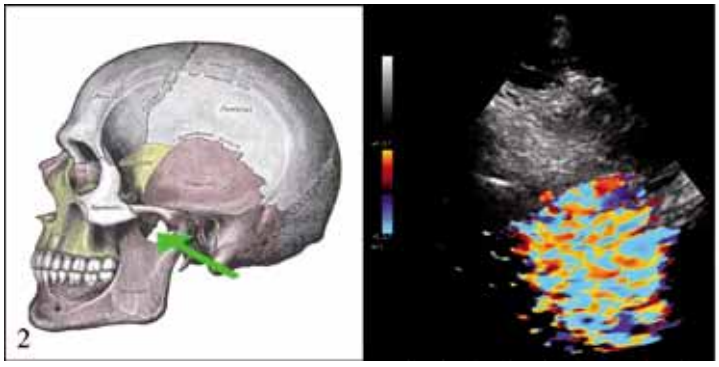

Figura 2.—Color cloud artifact marker of the trans-condylar approach.

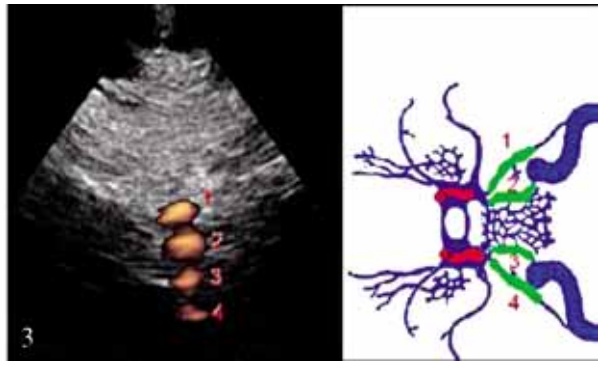

Figura 3.—Visualization of the power Doppler signal through the transcondylar window..

transducer should be placed at the level of the mandibular condyle, sloping the tail approximately 10 degree downward with the insonation depth adjusted to 11 cm. Deep inspiration should elicit venous flow at the depth of about 7 cm. This manoeuvre helps to identify a cloud composed by color Doppler signals, sometimes within an hyperechoic bright-line representing the sinus wall, visible immediately below the color flow dynamic image (Figure 2). Due to the lack of clearly visible anatomical B-Mode reference markers, the Color Doppler has to be activated from the beginning of the intracranial examination. At the low PRF set, such huge color cloud artifact indicates to the operator the right positioning of the probe. After this color cloud is detected, the operator has to increase the PRF and, eventually, to activate the Power Doppler, in order to have a better Color Doppler signal spatial definition (Figure 3).

This novel approach to the veins of the base of the skull may more constantly insonate venous flow without anatomical reference to structures of the brain parenchyma. One has the possibility to examine according to the depth of insonation the Superior Petrosal Sinus, the Inferior Petrosal Sinus, and the contralateral Inferior Petrosal Sinus (Figure 3). Sometimes the Cavernous Sinus, the Intercavernous Sinus, and, even more rarely, the Vein of Rosenthal and Basilar Plexus can be insonated.[62]

Because the PW angle of insonation is not favorable from the condylar approach, a multiangle Doppler system composed by more than 250 Doppler sample has been developed (QDP system, Esaote Biomedica, Genoa, Italy). Through a software algorithm it is possible to clearly detect the flow direction within the insonated venous structures.[15, 58, 62]

APPENDIX 7

Recommendations for postintervention follow-up

Follow-up, post-treatment ultrasound guidelines (as a strong recommendation of the faculty) to detect restenosis:

1) After 24 hours - review by ultrasound to rule out thrombus;
2) one month post-treatment - review by ultrasound;
3) three-months post-treatment - review by ultrasound;
4) six-months post-treatment - review by ultrasound;
5) nine-months post-treatment - review by ultrasound.