

Recommendations for Multimodal Noninvasive and Invasive Screening for Detection of Extracranial Venous Abnormalities Indicative of Chronic Cerebrospinal Venous Insufficiency: A Position Statement of the International Society for Neurovascular Disease

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Appendices A–D, Figures E1–E12, and Tables E1–E3 are available online at www.jvir.org.

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Under the auspices of the International Society for Neurovascular Disease (ISNVD), four expert panel committees were created from the ISNVD membership between 2011 and 2012 to determine and standardize noninvasive and invasive imaging protocols for detection of extracranial venous abnormalities indicative of chronic cerebrospinal venous insufficiency (CCSVI). The committees created working groups on color Doppler ultrasound (US), magnetic resonance (MR) imaging, catheter venography (CV), and intravascular US. Each group organized a workshop focused on its assigned imaging modality. Non-ISNVD members from other societies were invited to contribute to the various workshops. More than 60 neurology, radiology, vascular surgery, and interventional radiology experts participated in these workshops and contributed to the development of standardized noninvasive and invasive imaging protocols for the detection of extracranial venous abnormalities indicative of CCSVI. This ISNVD position statement presents the MR imaging and intravascular US protocols for the first time and describes refined color Doppler US and CV protocols. It also emphasizes the need for the use of noninvasive and invasive multimodal imaging to diagnose adequately and monitor extracranial venous abnormalities indicative of CCSVI for open-label or double-blinded, randomized, controlled studies.

ABBREVIATIONS

CCSVI = chronic cerebrospinal venous insufficiency, CNS = central nervous system, CSA = cross-sectional area, CV = catheter venography, IJV = internal jugular vein, ISNVD = International Society for Neurovascular Disease, MS = multiple sclerosis, PREMise = Prospective Randomized Endovascular Treatment in Multiple Sclerosis, VH = venous hemodynamic, VV = vertebral vein

The extracranial venous drainage of the cerebrospinal nervous system is complex, not widely examined, and only partially understood (1,2). It is often asymmetric and presents significantly more variability than the extracranial arterial anatomy that supplies the central nervous system (CNS). Contrary to other venous territories, relatively little is known about anatomic variations and the hemodynamics of the internal jugular veins (IJVs) (2,3), and even less is known about the azygos vein (4). Currently, disagreement remains about the physiologic range of hemodynamic measurements in these veins, including determination of normal or abnormal function. The walls of the IJVs and azygos vein are typically very compliant, with lumen diameters that are variable and influenced by postural change, respiration, cardiac function, hydration status, and even by the pulsation of nearby arteries (5,6). When imaging the extracranial venous drainage of the CNS, it is difficult to confidently account for all these factors, and this can influence the diagnostic value of the assessment, regardless of the imaging modality used.

Chronic cerebrospinal venous insufficiency (CCSVI) is a condition characterized by impaired venous drainage of the brain and spinal cord as a result of outflow obstruction in the extracranial venous system caused by stenoses or obstructions of the IJVs and/or azygos vein. Currently, its noninvasive diagnosis is based on the color Doppler ultrasound (US) evaluation of five venous hemodynamic (VH) criteria in the extracranial (ie, neck) and intracranial veins (4). The initial study found that two or more of the five proposed criteria were met in a high proportion of patients with multiple sclerosis (MS) (4). However, subsequent studies demonstrated that the condition is not unique to patients with MS and that healthy indi-

viduals and patients with other CNS disorders can also fulfill multiple VH criteria (7–13). Conversely, several recent color Doppler US studies reported extremely low rates of CCSVI, diagnosed based on two or more positive color Doppler US criteria, in patients with MS and healthy individuals (14–20).

Because the reproducibility of the categoric CCSVI color Doppler US-based diagnosis depends on the training level and skills of the operator and blinding and reading criteria (7,8,20–23), the usefulness and applicability of the CCSVI color Doppler US-based diagnosis in clinical research and practice is limited. Moreover, because healthy individuals do not have CNS disorders, its clinical relevance as a nosologic entity was immediately questioned (24). CCSVI implies a pathologic condition or disorder characterized by extracranial venous structural/morphologic, hemodynamic/functional abnormalities. Whether this condition is primarily characterized by clinical symptoms, such as headache, fatigue, sleep disturbances, and autonomic dysfunctions that can be improved by using endovascular treatment is unclear at this time (25).

A variety of other noninvasive and invasive imaging modalities have been proposed for the screening and diagnosis of CCSVI (5). In addition to color Doppler US, magnetic resonance (MR) imaging, specifically MR venography, has been proposed as a screening examination for CCSVI (8,16,26–31). MR venography allows noninvasive visualization of the entire venous system of the neck, central chest veins, brachiocephalic veins, and dural sinuses, but it cannot satisfactorily evaluate the azygos and hemiazygous veins (5). Catheter venography (CV) is considered the invasive gold-standard method for visualization of the IJVs and

azygos vein, but it may not identify intraluminal pathologic conditions because the density of injected contrast media may obscure intraluminal abnormalities (4,13,31–33). More recently, intravascular US is emerging as an important diagnostic tool for detection of venous abnormalities indicative of CCSVI (32–37).

In a recent debate article, Zivadinov and Chung (25) emphasize that one of the central issues regarding CCSVI to be further investigated is the definition of a significant narrowing of the extracranial venous system with hemodynamic consequences for the intracranial venous drainage. They critically report that the current definition (narrowing of > 50% in respect to the proximal adjacent vein segment) is mainly derived from observations in the arterial system and is therefore probably inadequate for the venous system. Probably even more important is to establish what constitutes a significant narrowing of the extracranial venous system with hemodynamic consequences for the intracranial venous drainage. Therefore, at this time, there is no established noninvasive or invasive diagnostic imaging modality that can serve as a gold standard for the detection of the extracranial venous abnormalities indicative of CCSVI (14,15,17,20,38). It is possible that a more appropriate choice of stenosis of hemodynamic consequence will be rather a fixed value for absolute cross-sectional area (CSA). Nevertheless, more sophisticated and validated multimodal imaging criteria are needed to adequately assess the clinical impact of extracranial venous abnormalities indicative of CCSVI for CNS pathologic conditions.

The present ISNVD reports for the first time recommended standardized noninvasive and invasive imaging protocols for evaluating extracranial venous abnormalities indicative of CCSVI.

METHODS

Under the auspices of ISNVD, four committees were created from the ISNVD membership between 2011 and 2012 to determine and standardize noninvasive and invasive imaging protocols for detection of extracranial venous abnormalities indicative of CCSVI. The four committees were composed of authorities with expertise in color Doppler US, MR venography, CV and intravascular US, respectively. The composition of the committees and their chairmen and relative members is described in the Acknowledgments. The selection criteria for committee members included previously published peer-reviewed manuscripts in the area of their expertise.

Each committee created a working group that organized workshops focused on their assigned imaging modality. Workshop participants were selected based on their scientific background and active use of the specific imaging modality. Non-ISNVD members from

other societies, including the International Union of Phlebology, International Union of Angiology, European Venous Forum, American College of Phlebology, Australian College of Phlebology, Italian Society of Angiology and Vascular Pathology, and Italian Society for Vascular Surgery, were invited to contribute to the various workshops. More than 60 neurology, radiology, vascular surgery, and interventional radiology experts participated in these workshops and contributed to the development of standardized noninvasive and invasive imaging protocols for detection of extracranial venous abnormalities indicative of CCSVI.

The relative workshops were held at the first ISNVD meeting in 2011 in Bologna, Italy; at the second ISNVD meeting in 2012 in Orlando, Florida; and at the third ISNVD meeting in 2013 in Krakow, Poland. Each committee created a preliminary draft that was shared by email in the 3 months preceding the conference to all invited and/or nominated members. The chairman and the scientific secretariat gathered all revisions and critical points reported in a second document that was publicly discussed at each workshop. All revisions to the initial document and subsequent drafts were discussed and voted on until a consensus was reached. If no consensus was reached, the critical points on which consensus was not reached were excluded from the document or it was emphasized that the debatable points require more research. Finally, the chairman and committee members drew up a third document for further revisions and final approval or comments. During the 3-year process, two position statements focused on two imaging modalities were developed and published by ISNVD (22,23,39). The color Doppler US position statement was published in two scientific journals respectively listed in the neuroscience and in the vascular disease ranking (22,23), whereas the CV position statement was published in a vascular disease ranking journal (39).

The present ISNVD document further refines these two position statements on color Doppler US and CV and presents for the first time the recommended MR imaging and intravascular US protocols for evaluating extracranial venous abnormalities indicative of CCSVI. The ISNVD is basing their recommendations on currently available literature. However, in cases in which there was no available literature, the recommendations are based only on experience of the workshop participants.

PROTOCOL FOR HIGH-RESOLUTION COLOR DOPPLER US

Rationale

Because color Doppler US is noninvasive and provides high-resolution images with real-time, dynamic interrogation of structural/morphologic and hemodynamic/functional venous abnormalities at relatively low cost, it

was initially proposed as a method of choice for the screening of CCSVI (4).

Imaging Technique

High-resolution color Doppler US is a noninvasive method that has been proposed for determining extracranial venous abnormalities indicative of CCSVI by assessing five VH characteristics (**Appendix A**, available online at www.jvir.org). (4) At least two of five criteria must be met to diagnose CCSVI by color Doppler US. The original five color Doppler US criteria for CCSVI (4) were revised by the ISNVD in 2011 (22,23), and are currently modified as follows:

1. Reflux in the IJV and/or vertebral veins (VVs) (4,8–10,12,15,20,35):
 - a. Bidirectional flow in one or both IJVs in both positions (supine and upright) or bidirectional flow in one position with absence of flow in the other position;
 - b. Reversal of flow or bidirectional flow in one or both VVs in both positions.
2. IJV stenosis (8–10,12,15,35):
 - a. Reduction of proximal IJV CSA in supine position to no more than 0.3 cm², which does not increase with Valsalva maneuver (performed at the end of the examination). Reduction of CSA of other parts of the IJV may be of clinical relevance, but abnormal cutoff values need further exploration, except for a complete or nearly complete occlusion of the vein;
 - b. Structural abnormalities, ie, intraluminal defects such as flaps, septa, or malformed valves combined with hemodynamic changes (flow arrest, reflux, increased blood flow velocity), and immobility of the valve leaflets confirmed by M-mode imaging.
3. Absence of detectable flow in the IJVs and/or VVs despite numerous deep inspirations and bidirectional flow detected in the other position on the same side (8–10,12,15,35).
4. CSA of the IJV is greater in the sitting position than in the supine position or is essentially unchanged despite a change in position (8–10,12,35,40).
5. Bidirectional flow in the intracranial veins and sinuses (recommended to be used as an additional criterion) (4).

Advantages

Color Doppler US has a significant role in the evaluation of CCSVI after endovascular treatment because it can show the effects of the treatment on the extracerebral venous outflow and can also recognize associated complications (eg, residual stenosis, venous thrombosis) (41,42).

Disadvantages

A number of studies showed that the recommended color Doppler US criteria for the diagnosis of CCSVI

are operator-dependent and that their reproducibility depends on the training level and skill of the operator, based on published studies (7,8,20–23). In addition to hemodynamic and morphologic assessment of IJVs and VVs, color Doppler US can detect extracranial collateral veins, which are probably a compensatory mechanism associated with CCSVI (2,8); however, it is not technically feasible to follow the complete course of collateral veins, which can be imaged by MR venography or CV (8,13,27,29–31,34).

Summary

In summary, color Doppler US provides a valuable diagnostic test, when applied by properly trained operators, for screening of CCSVI and further monitoring.

PROTOCOL FOR MR IMAGING

Rationale

Quantitative imaging of CCSVI with MR imaging provides an opportunity to study not just qualitative anatomic abnormalities such as stenosis of a major vein (8,16,18,26–31,43), but also the ability to quantify blood flow (**Appendix B**, available online at www.jvir.org). (26,28). These two pieces of information may provide new insights beyond those originally proposed by the CCSVI color Doppler US criteria (4). Specifically, recent MR imaging findings suggest that a relative reduction of total IJV flow normalized to the arterial inflow as measured from the carotid and vertebral arteries and an asymmetric dominance of IJV flow on one side of the neck may be identified in patients with MS (26).

Additional MR imaging research protocols that have been used to study CCSVI include angiographic, diffusion, iron content, oxygen saturation, perfusion, and cerebrospinal fluid estimations (**Appendix B**). Unfortunately, the complexity and length of these protocols make them largely impractical for use in a standard clinical setting. As a complement to the standard clinical neuroimaging protocol to assess MS and other neurologic diseases used by neurologists and neuroradiologists alike, a simple, rapid set of additional sequences to allow the extracranial vasculature to be assessed for anatomic and flow abnormalities should be established. These noninvasive measures provide validation of and are complementary to the color Doppler US measures.

Imaging Technique

A standard brain and spinal cord MR imaging protocol to study extracranial venous abnormalities, indicative of CCSVI is given in **Table E1** of **Appendix B** (available online at www.jvir.org). This MR protocol is based on the Consortium of Multiple Sclerosis Centers consensus guidelines for MR studies in patients with MS (44) and uses an intravenous contrast agent for the initial evaluation. Subjects returning for another MR scan may

or may not have a contrast agent used. Based on this standard clinical imaging protocol, the ISNVD suggests creation of two modified CCSVI MR imaging protocols that will provide a rapid basic assessment of venous anatomy and flow, in addition to standard evaluation of the brain and spinal cord. The Tier 1 protocol does not use a contrast agent, whereas the Tier 2 examination does use a contrast agent. The proposed scans are two-dimensional time-of-flight (TOF) MR venography, time-resolved contrast-enhanced three-dimensional MR angiography and venography, phase-contrast flow data at different levels in the neck, as well as the conventional T2-weighted imaging, fluid-attenuated inversion recovery and pre- and postcontrast T1-weighted magnetization-prepared rapid gradient-echo imaging (8,16,18,26–31,43). Both protocols are rapid, adding only a few minutes onto the conventional imaging times. As such, the ISNVD recommends that these MR imaging protocols are adopted into clinical settings engaged in the diagnosis and monitoring of CCSVI.

Advantages

A major benefit of the use of MR imaging for assessment of extracranial venous abnormalities indicative of CCSVI is that it provides the radiologist and interpreting physician with an assessment of the brain and spinal-cord pathologic conditions in the CNS. At the same time, it provides the interventionalist with a three-dimensional MR venographic map that completely displays the anatomy of any extracranial venous abnormalities to help guide management decisions and preprocedure treatment planning. (5) In general, MR imaging is operator-independent, and similar protocols can be performed on most clinically MR imaging systems. The data are also easily reproduced when performed on the same equipment from site to site.

Potential markers for extracranial venous abnormalities, indicative of CCSVI, can be identified from the collected data. MR imaging can longitudinally track the progress of the CNS disease over time by monitoring lesion character and volume, tissue atrophy, iron, diffusion, and perfusion and physiologic changes like blood flow and cerebrospinal fluid dynamics, and provide a baseline for future scans.

Disadvantages

However, there are practical concerns regarding the implementation of these protocols. Radiologists and interpreting physicians must be adequately trained to interpret the images. As with any imaging protocol, the reader must understand the technical limitations of the methodology and must have knowledge of the appropriate metrics to be analyzed from the quantitative data created from the examination.

Summary

MR imaging offers an important set of measures for radiologists, interpreting physicians, and interventionalists to aid in the detection and treatment of CCSVI. Diagnosticians must be facile with the appropriate protocols and metrics and should be familiar with the benefits and limitations of each protocol used.

PROTOCOL FOR CV

Rationale

Assessment of CV imaging of veins draining the CNS adheres to the traditional guidelines for angiographic interpretation used for examinations of arteries and other veins. The majority of CCSVI pathology is confined to the intraluminal portion of extracranial veins, which requires high-resolution color Doppler US or intravascular US B-mode imaging for the visualization of these anomalies (4,32,33,35–37). Although CV is considered to be the gold-standard method for detecting stenosis in blood vessels associated with altered blood flow, the recent results from Prospective Randomized Endovascular Treatment in MS (PREMiSe) study (45) showed that CV may not be sensitive enough to reveal the exact nature of narrowed vein segments (32,33). Being a luminogram, a CV image may yield little or no data regarding the vessel's intraluminal structures because of dense opacification of the lumen with contrast medium (39). The diluted contrast medium may allow a better visualization of endoluminal structures (eg, valve leaflets, webs), whereas nondiluted contrast medium allows a better opacification of epidural and other collateral vessels, as well as a better estimation of overall features of the veins (34). CV is sensitive in depicting the extraluminal structural/morphologic abnormalities that include narrowing and annulus (5,25).

It is important to acknowledge that there is incomplete understanding of the anatomy and physiology of the flow dynamics of the IJVs and the azygos vein, and, for this reason, it is difficult to reach a consensus on how to examine these veins and how to interpret the images obtained during CV. Committee members emphasized that CV of the IJVs and azygos vein is actually a “tarnished” gold standard, because even though CV is widely accepted as the main diagnostic tool for the assessment of extracranial venous abnormalities indicative of CCSVI, significant differences exist among cardiovascular centers in terms of venographic technique and interpretation of this test (4,13,14,30–32,34,46–48). There are some venographic appearances that the committee could not agree on, such as whether a diameter narrowing greater than 50% constitutes an abnormality (4,13).

An expert panel of the ISNVD published a position statement on the assessment of extracranial veins with details on the technical aspects of CV of the IJVs and azygos vein and key issues on the interpretation of the venographic images (39).

Imaging Technique

Regarding detection of the extracranial venous abnormalities indicative of CCSVI, the committee agreed on the general principles of angiographic procedural techniques (**Appendix C**, available online at www.jvir.org), but they still varied significantly in terms of the details of image interpretation. Because of these disagreements, a standard and widely accepted venographic protocol for the diagnosis of CCSVI has not been formally established. However, the panel experts agreed that further research is necessary and that a detailed description of the methods used for venographic evaluation and image interpretation will need to be specified in future publications on the topic (39). The inability to establish a consensus on CV is underscored by the lack of scientific evidence supporting a particular angiographic technique or protocol to guide interpretation of venographic images.

In patients with venographically evident lesions indicative of CCSVI, coexisting hemodynamically relevant lesions of the veins that are not draining the CNS directly (eg, iliac, renal, or ascending lumbar veins) may be identified (2,4). The clinical relevance of these abnormalities in terms of any association with neurologic pathophysiology remains uncertain. In addition, stenoses of cerebral sinuses and intracranial veins are other potential coexisting findings.

Advantages

CV is the gold-standard method for imaging veins. It is a commonly performed low-risk procedure with a safety record established over decades of experience (4,13,14,30–32,34,46,47,49).

Disadvantages

Many veins examined by CV display a less obvious luminal stenosis or functional abnormality. Currently, some interventionalists would interpret these findings as pathologic (eg, intraluminal structures, such as valve leaflets that may or may not be associated with venographic signs of compromised outflow), whereas others would regard such findings as normal (50). More detailed classification of intraluminal and extraluminal extracranial venous abnormalities and their frequency is provided in a recently published debate article by Zivadinov and Chung (25).

Uncertainties related to the use of CV for detection of extracranial venous abnormalities indicative of CCSVI can be grouped into several domains: the preferred vascular access for CV, the ideal dilution of contrast media used, definition of reflux during contrast agent injection, interpretive guidelines (including whether venous diameter and anatomy of accompanying venous collateral network should be taken into account), time (in seconds) of delayed emptying of the interrogated vein (51), the definition of a pathologic valve and other abnormal intraluminal structures, whether intravascu-

lar US should accompany a routine CV evaluation for CCSVI, whether a phasic stenosis (ie, a narrowing that is transient or dynamic) should be regarded as a normal variant or pathologic, and how to classify venographically obvious CCSVI lesions (13,32,34–37,39).

Summary

Given the lack of a scientific validation for any given CV protocol, it has been recommended that any future publication on extracranial venous abnormalities indicative of CCSVI that deals with angiographic assessment should include a detailed description of the technique used and a definition of pathologic findings. Most of the published papers on CCSVI lack these details, which limits a rigorous analysis of presented data (4,13,14,30–32,34,46–48,52). It is hoped that a detailed description of CV in a manner similar to that proposed by the ISNVD CCSVI CV protocol accompany future publications to enable a better comparison of study results.

PROTOCOL FOR INTRAVASCULAR US

Rationale

Intravascular US is proposed as an additional procedure that can provide further information regarding extracranial venous structural abnormalities indicative of CCSVI (37). Compared with CV, its high image resolution provides a more detailed view of the lumen. In addition, intravascular US can provide information about the azygos vein, as well as intraluminal lesions such as webs, septum, or immobile valves, which are frequently difficult to detect by CV (37).

Intravascular US can provide diagnostic details that may address many of the diagnostic deficiencies that elude detection by color Doppler US, MR venography, and CV (32–37). Intravascular US is useful in characterization of the vessel wall and the endothelium. In addition, intravascular US presents a real-time cross-sectional view that allows visualizations of possible stenoses during a variety of physiologic maneuvers such as Valsalva and reverse Valsalva, inspiration and expiration cervical, flexion and extension, and varying degrees of neck rotation (53). Neglen and Raju (54) have argued effectively for the use of intravascular US in chronic iliac venous stenosis and occlusions. They frequently recognized an irregular shape of the iliac vein, and, consequently, the difficulties in using diameter determinations from a single projectional venographic view to make stenosis measurements. They point out that cross-sectional morphology may provide prognostic value in terms of accurately predicting clinical improvement after balloon angioplasty. Further, they emphasize that intraluminal abnormalities, such as immobile valves, subintimal edema, and echogenic material (eg, trabeculae, septa, and webs) cannot be seen by CV (54).

Imaging Technique

To standardize intravascular US application across centers, the ISNVD expert committee on intravascular US proposed a CCSVI intravascular US protocol (**Appendix D**, available online at www.jvir.org). Intravascular US may be indicated in CCSVI for the detection of intraluminal venous pathologic conditions, for stenosis analysis, as an aid for assessing dynamic or atypical narrowings, and as an interventional postangioplasty examination (32–37). In unusual circumstances, intravascular US enables diagnostic and therapeutic procedures without the use of iodinated contrast media. This is particularly relevant in the evaluation and treatment of patients who have had potentially life-threatening allergic reactions to contrast media or who have severe renal insufficiency.

Advantages

The frequency of intraluminal lesions in patients with extracranial venous abnormalities indicative of CCSVI suggests that an intraluminal imaging study is appropriate for the complete diagnosis of this pathologic condition. CV can demonstrate the major stenotic lesions, but superimposition of valvular cusps and reflux opacification of the vessel distal to a stenosis may obscure the evaluation of valvular narrowing (32–37). Moreover, CV cannot distinguish the various etiologies of such stenoses. Abnormal valves characterized by echogenic irregular thickening, poor mobility, and bulging cusps, as well as an accompanying septum and/or webs, are more easily seen by intravascular US because these features are highly echogenic. Neglen and Raju (54) have published evidence that such a venous pathologic state in the iliac vein is unrecognized by venography and yet it is well seen by intravascular US. Most recently, Karmon et al (32) described intravascular US findings of intraluminal hyperechoic filling defects and parallel double-barrel lumens in the veins of patients with MS. In addition, the results from the PREMise study (45) showed that CV may not be sensitive enough to reveal the exact nature of narrowed IJV segments (32,33). Another major advantage of intravascular US is that a vein can be imaged in a specific area, having the patient change the position of the head and determine if a stenosis is a true stenosis or an effect of a compression (especially at the level of the thyroid gland) (34).

Finally, intravascular US provides an excellent means of evaluating the effectiveness of venoplasty and valvuloplasty. The opening of immobile valves is particularly well appreciated by intravascular US. In addition, complications of angioplasty, such as thrombus and dissection, are readily identified with intravascular US.

Disadvantages

There is little published in the medical literature about the use of intravascular US in the IJV and the azygos

vein (32–37). The sensitivity of intravascular US can be affected by the frequency of the transducer, gain settings, depth of penetration, and focal depth (5,37).

Summary

Additional research should be focused on improving resolution of the transducer/detector, developing the capability to measure flow and pressure, and analyzing the accuracy of intravascular US.

DISCUSSION

The difference in CCSVI prevalence between different published studies that use noninvasive or invasive imaging techniques emphasizes the urgent need for the use of a multimodal imaging approach for better understanding of the venous abnormalities indicative of CCSVI (5). Multimodal studies that use noninvasive and invasive imaging techniques to detect CCSVI are rapidly emerging (4,8,13,14,16,27,30–36,38,48). The findings of these studies are important to better understand the actual prevalence of extracranial venous abnormalities indicative of CCSVI in patients with MS, healthy individuals, and patients with other CNS disorders. Most of the recent invasive studies that used intravascular US suggest that the frequency of extracranial venous abnormalities indicative of CCSVI may be higher than previously reported (32–37). For example, in a recent article, Zivadinov et al (33) evaluated the two noninvasive and two invasive multimodal imaging correlates of 20 patients with relapsing MS who were enrolled in the PREMise study (45). They concluded that a noninvasive and invasive multimodal imaging diagnostic approach should be recommended to depict a range of extracranial venous abnormalities indicative of CCSVI. In another study, Traboulsee et al (13) reported that 74% of patients with MS, 70% of healthy control subjects, and 66% of unaffected siblings of patients with MS showed greater than 50% narrowing on the CV in at least one of these three extracranial veins. These findings contradict a number of recent color Doppler US studies that report an extremely low prevalence of CCSVI in patients with MS (14,15,17,20,38).

The ISNVD recommends a multimodal noninvasive and invasive approach to determine what is the true prevalence of CCSVI in patients with MS and other CNS disorders, as well as in healthy individuals. The proposed imaging protocols were created with the contributions of more than 60 neurology, radiology, vascular surgery, and interventional radiology experts who participated in the ISNVD workshops held at the ISNVD Annual Meetings between 2011 and 2013. The ISNVD understands that more multimodal validation studies should be performed before the firm recommendations about the best combination of different imaging techniques for diagnosis

and monitoring of extracranial venous abnormalities indicative of CCSVI can be proposed. In the meantime, the ISNVD recommends that at least one noninvasive and one invasive technique should be performed to detect extracranial venous abnormalities indicative of CCSVI. Use of noninvasive multimodal imaging is recommended for monitoring purposes.

CONCLUSIONS

Although some CNS disorders have been linked to the presence and severity of CCSVI, the ultimate cause–consequence relationship has not been firmly established (25). Therefore, it is not clear at this time which patient population should undergo the noninvasive and invasive studies for detection of extracranial venous abnormalities. The ISNVD recommends the use of a multimodal noninvasive and invasive imaging approach to optimally identify extracranial venous structural/morphologic and hemodynamic/functional abnormalities indicative of CCSVI. Creation of more quantitative imaging criteria are needed for further characterization of these venous abnormalities. Screening and monitoring of these venous abnormalities with the use of a combined noninvasive and invasive imaging approach should help establish the actual incidences and prevalence of extracranial venous abnormalities indicative of CCSVI in various populations. In addition, a multimodal imaging approach will address whether these abnormalities can cause significant hemodynamic consequences for intracranial venous drainage. The proposed noninvasive and invasive imaging protocols represent a first step toward establishing and validating the criteria for detection and monitoring of extracranial venous abnormalities indicative of CCSVI in open-label or double-blinded randomized controlled studies. The ISNVD recognizes that the rapidly evolving science and growing interest in this field will facilitate a refinement of these protocols in the near future.

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REFERENCES

- Burrows PE, Konez O, Bisdorff A. Venous variations of the brain and cranial vault. *Neuroimaging Clin N Am* 2003; 13:13–26.
- Zamboni P, Consorti G, Galeotti R, et al. Venous collateral circulation of the extracranial cerebrospinal outflow routes. *Curr Neurovasc Res* 2009; 6:204–212.
- Schreiber 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; 94:1802–1805.
- Zamboni P, Galeotti R, Menegatti E, et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2009; 80:392–399.
- Dolic K, Siddiqui AH, Karmon Y, Marr K, Zivadinov R. The role of noninvasive and invasive diagnostic imaging techniques for detection of extra-cranial venous system anomalies and developmental variants. *BMC Med* 2013; 11:155.
- Chung CP, Hsu HY, Chao AC, Wong WJ, Sheng WY, Hu HH. Flow volume in the jugular vein and related hemodynamics in the branches of the jugular vein. *Ultrasound Med Biol* 2007; 33:500–505.
- Zivadinov R, Marr K, Cutter G, et al. Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS. *Neurology* 2011; 77:138–144.
- Dolic K, Marr K, Valnarov V, et al. Sensitivity and specificity for screening of chronic cerebrospinal venous insufficiency using a multimodal non-invasive imaging approach in patients with multiple sclerosis. *Funct Neurol* 2011; 26:205–214.
- Garaci FG, Marziali S, Meschini A, et al. Brain hemodynamic changes associated with chronic cerebrospinal venous insufficiency are not specific to multiple sclerosis and do not increase its severity. *Radiology* 2012; 265:233–239.
- Mancini M, Morra VB, Di Donato O, et al. Multiple sclerosis: cerebral circulation time. *Radiology* 2012; 262:947–955.
- Monti L, Menci E, Ulivelli M, et al. Quantitative colour Doppler sonography evaluation of cerebral venous outflow: a comparative study between patients with multiple sclerosis and controls. *PLoS One* 2011; 6:e25012.
- Patti F, Nicoletti A, Leone C, et al. Multiple sclerosis and CCSVI: a population-based case control study. *PLoS One* 2012; 7:e41227.
- Traboulsee AL, Knox KB, Machan L, et al. Prevalence of extracranial venous narrowing on catheter venography in people with multiple sclerosis, their siblings, and unrelated healthy controls: a blinded, case-control study. *Lancet* 2014; 383:138–145.
- 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; 69:90–99.
- Doepp F, Paul F, Valdueza JM, Schmierer K, Schreiber SJ. No cerebrocervical venous congestion in patients with multiple sclerosis. *Ann Neurol* 2010; 68:173–183.
- Doepp F, Wurfel JT, Pfueller CF, et al. Venous drainage in multiple sclerosis: a combined MRI and ultrasound study. *Neurology* 2011; 77:1745–1751.
- Comi G, Battaglia MA, Bertolotto A, et al. Observational case-control study of the prevalence of chronic cerebrospinal venous insufficiency in multiple sclerosis: results from the CoSMo study. *Mult Scler* 2013; 19:1508–1517.
- Macgowan CK, Chan KY, Laughlin S, Marrie RA, Banwell B. Cerebral arterial and venous blood flow in adolescent multiple sclerosis patients and age-matched controls using phase contrast MRI. *J Magn Reson Imaging* 2014; 40:341–347.

19. Rodger IW, Dilar D, Dwyer J, et al. Evidence against the involvement of chronic cerebrospinal venous abnormalities in multiple sclerosis. A case-control study. *PLoS One* 2013; 8:e72495.
20. Tsvigoulis G, Mantatzis M, Bogiatzi C, et al. Extracranial venous hemodynamics in multiple sclerosis: a case-control study. *Neurology* 2011; 77:1241–1245.
21. Menegatti E, Genova V, Tessari M, et al. The reproducibility of colour Doppler in chronic cerebrospinal venous insufficiency associated with multiple sclerosis. *Int Angiol* 2010; 29:121–126.
22. Nicolaides AN, Morovic S, Menegatti E, Viselner G, Zamboni P. Screening for chronic cerebrospinal venous insufficiency (CCSVI) using ultrasound: recommendations for a protocol. *Funct Neurol* 2011; 26:229–248.
23. Zamboni P, Morovic S, Menegatti E, Viselner G, Nicolaides AN. Screening for chronic cerebrospinal venous insufficiency (CCSVI) using ultrasound—recommendations for a protocol. *Int Angiol* 2011; 30:571–597.
24. Khan O, Filippi M, Freedman MS, et al. Chronic cerebrospinal venous insufficiency and multiple sclerosis. *Ann Neurol* 2010; 67:286–290.
25. Zivadinov R, Chung CP. Potential involvement of the extracranial venous system in central nervous system disorders and aging. *BMC Med* 2013; 11:260.
26. Haacke EM, Feng W, Utraiainen D, et al. Patients with multiple sclerosis with structural venous abnormalities on MR imaging exhibit an abnormal flow distribution of the internal jugular veins. *J Vasc Interv Radiol* 2012; 23:60–68.
27. McTaggart RA, Fischbein NJ, Elkins CJ, et al. Extracranial venous drainage patterns in patients with multiple sclerosis and healthy controls. *AJNR Am J Neuroradiol* 2012; 33:1615–1620.
28. Sundstrom P, Wahlin A, Ambarki K, Birgander R, Eklund A, Malm J. Venous and cerebrospinal fluid flow in multiple sclerosis: a case-control study. *Ann Neurol* 2010; 68:255–259.
29. Wattjes MP, van Oosten BW, de Graaf WL, et al. No association of abnormal cranial venous drainage with multiple sclerosis: a magnetic resonance venography and flow-quantification study. *J Neurol Neurosurg Psychiatry* 2011; 82:429–435.
30. 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; 32:1482–1489.
31. Zivadinov R, Galeotti R, Hojnacki D, et al. Value of MR venography for detection of internal jugular vein anomalies in multiple sclerosis: a pilot longitudinal study. *AJNR Am J Neuroradiol* 2011; 32:938–946.
32. Karmon Y, Zivadinov R, Weinstock-Guttman B, et al. Comparison of intravascular ultrasound with conventional venography for detection of extracranial venous abnormalities indicative of chronic cerebrospinal venous insufficiency. *J Vasc Interv Radiol* 2013; 24:1487–1498.
33. Zivadinov R, Karmon Y, Dolic K, et al. Multimodal noninvasive and invasive imaging of extracranial venous abnormalities indicative of CCSVI: results of the PREMiSe pilot study. *BMC Neurol* 2013; 13:151.
34. Ferral H, Behrens G, Tumer Y, Riemenschneider M. Endovascular diagnosis and management of chronic cerebrospinal venous insufficiency: retrospective analysis of 30-day morbidity and mortality in 95 consecutive patients. *AJR Am J Roentgenol* 2013; 200:1358–1364.
35. Lugli M, Morelli M, Guerzoni S, Maletti O. The hypothesis of pathophysiological correlation between chronic cerebrospinal venous insufficiency and multiple sclerosis: rationale of treatment. *Phlebology* 2012; 27 (suppl 1):178–186.
36. Scalise F, Farina M, Manfredi M, Auguadro C, Novelli E. Assessment of jugular endovascular malformations in chronic cerebrospinal venous insufficiency: colour-Doppler scanning and catheter venography compared with intravascular ultrasound. *Phlebology* 2013; 28:409–417.
37. Sclafani SJ. Intravascular ultrasound in the diagnosis and treatment of chronic cerebrospinal venous insufficiency. *Tech Vasc Interv Radiol* 2012; 15:131–143.
38. Baracchini C, Perini P, Causin F, Calabrese M, Rinaldi F, Gallo P. Progressive multiple sclerosis is not associated with chronic cerebrospinal venous insufficiency. *Neurology* 2011; 77:844–850.
39. Simka M, Hubbard D, Siddiqui AH, et al. Catheter venography for the assessment of internal jugular veins and azygous vein: position statement by expert panel of the International Society for Neurovascular Disease. *Vasa* 2013; 42:168–176.
40. Zamboni P, Menegatti E, Galeotti R, et al. The value of cerebral Doppler venous haemodynamics in the assessment of multiple sclerosis. *J Neurol Sci* 2009; 282:21–27.
41. Zamboni P, Galeotti R, Menegatti E, et al. A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency. *J Vasc Surg*. 2009; 50:1348–1358.
42. 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* 2012; 43:116–122.
43. Zamboni P, Menegatti E, Viselner G, Morovic S, Bastianello S. Fusion imaging technology of the intracranial veins. *Phlebology* 2012; 27:360–367.
44. Simon JH, Li D, Traboulsee A, et al. Standardized MR imaging protocol for multiple sclerosis: Consortium of MS Centers consensus guidelines. *AJNR Am J Neuroradiol* 2006; 27:455–461.
45. Siddiqui AH, Zivadinov R, Benedict RH, et al. Prospective randomized trial of venous angioplasty in MS (PREMiSe). *Neurology* 2014; 83:441–449.
46. Mandato K, Englander M, Keating L, Vachon J, Siskin GP. Catheter venography and endovascular treatment of chronic cerebrospinal venous insufficiency. *Tech Vasc Interv Radiol* 2012; 15:121–130.
47. 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; 18:314–323.
48. Simka M. New avenues of research on multiple sclerosis from the perspective of chronic cerebrospinal venous insufficiency paradigm. *Rev Recent Clin Trials* 2012; 7:81–82.
49. Simka M. Possible pathomechanisms responsible for injury to the central nervous system in the settings of chronic cerebrospinal venous insufficiency. *Rev Recent Clin Trials* 2012; 7:93–99.
50. Simka M, Latacz P, Ludya T, et al. Prevalence of extracranial venous abnormalities: results from a sample of 586 multiple sclerosis patients. *Funct Neurol* 2011; 26:197–203.
51. Veroux P, Giaquinta A, Perricone D, et al. Internal jugular veins out flow in patients with multiple sclerosis: a catheter venography study. *J Vasc Interv Radiol* 2013; 24:1790–1797.
52. Ludya T, Kazibudski M, Simka M, et al. Endovascular treatment for chronic cerebrospinal venous insufficiency: is the procedure safe? *Phlebology* 2010; 25:286–295.
53. Reid DB, Douglas M, Diethrich EB. The clinical value of three-dimensional intravascular ultrasound imaging. *J Endovasc Surg* 1995; 2:356–364.
54. Neglen P, Raju S. Intravascular ultrasound scan evaluation of the obstructed vein. *J Vasc Surg* 2002; 35:694–700.
55. Zamboni P, Morovic S, Menegatti E, Viselner G, Nicolaides AN. Screening for chronic cerebrospinal venous insufficiency (CCSVI) using ultrasound—recommendations for a protocol. *Int Angiol* 2011; 30:571–597.
56. Nicolaides AN, Morovic S, Menegatti E, Viselner G, Zamboni P. Screening for chronic cerebrospinal venous insufficiency (CCSVI) using ultrasound: recommendations for a protocol. *Funct Neurol* 2011; 26:229–248.
57. McDonald S, Icton JB. The use of Doppler ultrasound in the diagnosis of chronic cerebrospinal venous insufficiency. *Tech Vasc Interv Radiol* 2012; 15:113–120.
58. Zamboni P, Galeotti R, Menegatti E, et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2009; 80:392–399.
59. Baumgartner RW, Nirrko AC, Muri RM, Gonner F. Transoccipital power-based color-coded duplex sonography of cerebral sinuses and veins. *Stroke* 1997; 28:1319–1323.
60. Stolz E, Kaps M, Kern A, Babacan SS, Dorndorf W. Transcranial color-coded duplex sonography of intracranial veins and sinuses in adults. Reference data from 130 volunteers. *Stroke* 1999; 30:1070–1075.
61. Walter U. Transcranial sonography-assisted stereotaxy and follow-up of deep brain implants in patients with movement disorders. *Int Rev Neurobiol* 2010; 90:274–285.
62. Zamboni P, Menegatti E, Pomidori L, et al. Does thoracic pump influence the cerebral venous return? *J Appl Physiol* 2012; 112:904–910.
63. Zamboni P, Menegatti E, Viselner G, Morovic S, Bastianello S. Fusion imaging technology of the intracranial veins. *Phlebology* 2012; 27:360–367.
64. Ciccone MM, Galeandro AI, Scicchitano P, et al. Multigate quality Doppler profiles and morphological/hemodynamic alterations in multiple sclerosis patients. *Curr Neurovasc Res* 2012; 9:120–127.
65. Dolic K, Siddiqui AH, Karmon Y, Marr K, Zivadinov R. The role of noninvasive and invasive diagnostic imaging techniques for detection of extra-cranial venous system anomalies and developmental variants. *BMC Med* 2013; 11:155.
66. Mancini M, Morra VB, Di Donato O, et al. Multiple sclerosis: cerebral circulation time. *Radiology* 2012; 262:947–955.
67. Simon JH, Li D, Traboulsee A, et al. Standardized MR imaging protocol for multiple sclerosis: Consortium of MS Centers consensus guidelines. *AJNR Am J Neuroradiol* 2006; 27:455–461.
68. Dolic K, Marr K, Valnarov V, et al. Sensitivity and specificity for screening of chronic cerebrospinal venous insufficiency using a multimodal non-

- invasive imaging approach in patients with multiple sclerosis. *Funct Neurol* 2011; 26:205–214.
69. Dolic K, Marr K, Valnarov V, et al. Intra- and extraluminal structural and functional venous anomalies in multiple sclerosis, as evidenced by 2 noninvasive imaging techniques. *AJNR Am J Neuroradiol* 2012; 33:16–23.
 70. Hojnacki D, Zamboni P, Lopez-Soriano A, et al. Use of neck magnetic resonance venography, Doppler sonography and selective venography for diagnosis of chronic cerebrospinal venous insufficiency: a pilot study in multiple sclerosis patients and healthy controls. *Int Angiol* 2010; 29:127–139.
 71. Zivadinov R, Galeotti R, Hojnacki D, et al. Value of MR venography for detection of internal jugular vein anomalies in multiple sclerosis: a pilot longitudinal study. *AJNR Am J Neuroradiol* 2011; 32:938–946.
 72. Zivadinov R, Lopez-Soriano A, Weinstock-Guttman B, et al. Use of MR venography for characterization of the extracranial venous system in patients with multiple sclerosis and healthy control subjects. *Radiology* 2011; 258:562–570.
 73. McTaggart RA, Fischbein NJ, Elkins CJ, et al. Extracranial venous drainage patterns in patients with multiple sclerosis and healthy controls. *AJNR Am J Neuroradiol* 2012; 33:1615–1620.
 74. 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; 32:1482–1489.
 75. Feng W, Utraiainen D, Trifan G, Sethi S, Hubbard D, Haacke E. Quantitative flow measurements in the internal jugular veins of multiple sclerosis patients using magnetic resonance imaging. *Rev Recent Clin Trials* 2012; 7:117–126.
 76. Haacke EM, Feng W, Utraiainen D, et al. Patients with multiple sclerosis with structural venous abnormalities on MR imaging exhibit an abnormal flow distribution of the internal jugular veins. *J Vasc Interv Radiol* 2012; 23:60–68.
 77. Utraiainen D, Trifan G, Sethi S, et al. Magnetic resonance imaging signatures of vascular pathology in multiple sclerosis. *Neurol Res* 2012; 34:780–792.
 78. Sundstrom P, Wahlin A, Ambarki K, Birgander R, Eklund A, Malm J. Venous and cerebrospinal fluid flow in multiple sclerosis: a case-control study. *Ann Neurol* 2010; 68:255–259.
 79. Simka M, Hubbard D, Siddiqui AH, et al. Catheter venography for the assessment of internal jugular veins and azygous vein: position statement by expert panel of the International Society for Neurovascular Disease. *Vasa* 2013; 42:168–176.

APPENDIX A: HIGH-RESOLUTION COLOR DOPPLER ULTRASOUND CHRONIC CEREBROSPINAL VENOUS INSUFFICIENCY PROTOCOL

Equipment and Positioning

For the chronic cerebrospinal venous insufficiency (CCSVI) assessment, a high-end color Doppler ultrasound (US) scanning system equipped with two vascular US transducers is required (55–58). A linear-array broad-bandwidth probe suitable for superficial vascular imaging (7.5–13 MHz) is recommended to assess the extracranial neck veins (internal jugular veins [IJVs] and vertebral veins [VVs]). A phased-array transducer with a lower-frequency bandwidth (2–3 MHz) is recommended to investigate the deep cerebral veins and sinuses.

When visualization of the jugular–subclavian junction segment proves technically challenging, the use of a curvilinear/microconvex probe with a smaller footprint may be useful. The color-flow and spectral Doppler setting should be adjusted according to the guidelines and, in turn, optimized on each patient.

Attention should be paid especially to the pulse repetition frequency (PRF) and wall filter setting. The former has to be lowered to detect lower flow rates or increased to avoid aliasing when the actual velocities appear higher than predicted, and the latter has to be set to the detection of low velocity. Whereas the steering angle and color gain should be regulated to ensure the complete color filling of the vessel is under investigation.

When examining venous flow to include full range of velocities and all areas of reflux or absence of flow, the sample volume needs to be open completely for the entire lumen and must be placed in the centre of the vessel. The angle of insonation of the Doppler beam to the direction of flow should be 60°. However, this may be difficult to achieve in the IJV and VV without applying pressure on the skin by changing the angle of the probe, and reducing the angle down to 45° is acceptable. It is recommended to never use an angle greater than 60°.

The patient has to be comfortably positioned on an electromechanical chair or a standard tilt bed. The examination starts in the supine posture with the head in the natural position and always looking upward and forward. The patient should breathe normally through the nose, and no Valsalva maneuver is required. When the first phase is complete, the examination is repeated with the patient in the upright (90°) position, again keeping the head facing forward. Two or three minutes should be allowed for adaptation before starting after changing from the supine to the upright position. The patients should be well hydrated to avoid a negative impact on the filling of the veins (55–58).

Extracranial Examination

The extracranial examination begins on the right side, in the transverse plane, and, with the lightest possible pressure, it locates the jugular vein. A large amount of ultrasonic gel should be used to avoid excessive pressure on the patient's neck that may change the shape and dimension of the IJV and to ensure complete coupling between the transducer and the patient's skin, avoiding black cones and dark areas on the image.

The IJV is then assessed at three different levels named J1, J2, and J3 (55,56):

J1 is the most inferior portion of the IJV and portion closest to the heart. It includes the inferior jugular bulb and the area of the confluents of the IJV with the subclavian vein to form the brachiocephalic vein;

J2 is the middle of the vein at the level of the thyroid gland and includes the orifice of the facial vein; and

J3 is the most superior portion of the IJV beginning near the angle of the mandible and extending to the skull base and superior jugular bulb.

B-Mode Evaluation. Starting from the base of the neck (ie, J1) to the angle of the jaw (ie, J3) a B-mode evaluation is performed. The search of the abnormalities should be primarily performed in the supine position because, in this hemodynamic situation, the jugular veins are physiologically dilated and it is easier to find a lesion or malformation. After evaluation in the transverse plane, the IJV has to be completely evaluated in the longitudinal plane. The most frequent area of an intraluminal abnormality obstacle is J1 because of the physiologic presence of the valve at the termination of the IJV just before its junction with the subclavian vein. The major abnormalities that can be found at the level of the IJV valve are a flap, septum, annulus, double channel, or anomalous orientation of the valve leaflets (eg, inverted position of the leaflets, leaflets positioned on the lateral side of the jugular wall). Additionally, and similarly to cardiac valve evaluation by echocardiography and/or in the deep venous system of the lower extremity, the M-mode may detect significant information about the mobility of the valve's cusps (immobile leaflets, immobility limited to one of the two leaflets).

Hemodynamic Evaluation. Hemodynamic evaluation requires verification by longitudinal imaging. Starting from the lower end of the middle segment of the IJV (ie, J2), the flow direction should be observed by means of color mode, asking the patient to breathe quietly through the nose. Subsequently, the flow direction and duration of reflux/bidirectional flow should be proven by means of a Doppler spectral analysis. The absence of flow in color Doppler mode should be confirmed by Doppler spectral analysis and absence of thrombosis by compression. This measurement is repeated at the levels of J3 and J1 as well.

It is suggested to insonate the lower part of the IJV (ie, J1) last, after careful evaluation of the J2 and J3 segments. Reflux or absence of flow may occur and can be detected in any segment of the IJV.

Measurements of Cross-Sectional Area. The cross-sectional area (CSA) measurements are performed in transverse B-mode scans of the middle segment (ie, J2) by using the appropriate area measuring tool and has to be recorded at the same point in supine and sitting positions. If the CSA in supine position is smaller than in the upright position, it is considered pathologic.

VV Examination. VVs have to be examined in visible segments (the easiest segment to be examined is between C5 and C6) 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. It is considered reflux when the vein flow has the same direction of the arterial one. This reversed flow, which is also considered as abnormal (ie, reflux), may be the result of activation of collateral vessels connecting extravertebral with intravertebral veins. Because, in many individuals, the VVs are tortuous, a “reversed” flow direction can be a reflexion of such an irregularity and not of actual reflux. Insonation of the vein in different locations may be helpful to resolve such a diagnostic problem.

Intracranial Examination

The cerebral venous system is usually investigated by means of transcranial access, usually through the temporal window; however, the transoccipital approach has also been described (59–61).

Both approaches provide satisfactory images and hemodynamic information, especially of the Rosenthal vein, and less frequently of the Galen vein and straight sinus (59–62).

However, it is very rare to find flow abnormalities in the veins through the aforementioned approaches. In fact, the intracranial veins cannot be modulated like the extracranial one by the activation of the respiratory pump, because the skull prevents any modulation of atmospheric pressure. In physiology, it has been proven that a standardized activation of the thoracic pump does not produce any significant changes in flow and velocity at the level of the parenchymal veins or of the sinuses (62).

For such a reason, an alternative approach through the condylar window has been validated by means of fusion imaging technology between magnetic resonance (MR) imaging and US (63). The US probe should be placed at the level of the condyloid process of the mandible, sloping the tail approximately 10° downward, with the insonation depth adjusted to 11 cm. A slight pressure right in the area of the patient’s cheekbone is normal. This level of pressure is necessary to maintain the probe

on the same position when the operator receives the Doppler signal of the cerebral veins topic of the examination. The US scanner should be set starting with a lower PRF value, which ranges from 370 to 500 kHz; deep inspiration should elicit venous flow at the depth of about 7 cm. This maneuver helps to identify a cloud composed by color Doppler US signals, sometimes within a hyperechoic bright-line representing the sinus wall, visible immediately below the color flow dynamic image. The PRF value is then increased to avoid disturbances caused by vibration produced from the close anatomic relationship of the sphenoid bone with the airways. Finally, a further assessment is performed by placing the Doppler pulse waved sample volume into the imaged color flow to confirm the presence of venous signal.

This approach allows insonation of the veins of the base of the skull according to the depth of insonation of the superior petrosal sinus, the inferior petrosal sinus, and the contralateral inferior and superior petrosal sinuses. 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 with the use of a multiangle Doppler system, such as the quality Doppler processing (QDP) technology (64). 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 to clearly visualize the direction without background Doppler noise. This technology is not available on all US scanning systems. For such reason, the ISNVD consensus stated that the intracranial examination must be considered as an additional criterion in the diagnosis of CCSVI (55,56).

Fulfilment of the CCSVI Diagnosis

The subject is assigned venous hemodynamic (VH) score calculated by counting the number of positive VH criteria the subject fulfilled (Figs E1–E5). A subject is considered CCSVI-positive if two or more than two VH criteria are fulfilled and CCSVI-negative if fewer than two VH criteria are fulfilled. Subjects who were not assessed for a VH criterion as a result of technical difficulty or the absence of ideal equipment (ie, QDP technology) are assumed to have not fulfilled that criterion. At this time, it is unknown whether the prevalence of CCSVI between patients with multiple sclerosis (MS) and healthy individuals, as well as patients with other central nervous system diseases, is similar to published literature when bidirectional flow in the intracranial veins and sinuses is excluded as additional criterion for the diagnosis of CCSVI (65).

Further Considerations

In addition, the color Doppler US committee discussed future consideration of two additional screening tests. One is a proprietary technology called QDP (10) designed to

insonate the veins at the base of the skull. In particular, it is difficult to visualize the superior petrosal sinus, the inferior petrosal sinus, and the contralateral inferior and superior petrosal sinuses. Because insonation of the petrosal sinuses requires a Doppler angle close to 90°, detection of reflux in the form of bidirectional flow can be made only by using a multiangle Doppler system. The QDP technology enables the operator to determine the direction of blood flow within the examined cerebral veins and make an adjustment of the PRF to clearly visualize the direction without background Doppler noise. Although this technology has been recently validated (63,64), it still has limited availability. Because of this, the committee determined that the intracranial examination of bidirectional flow in the intracranial veins and sinuses by using QDP technology can only be considered as an additional criterion for diagnosis of CCSVI (55,56). However, at this time, it is unknown whether the addition of this technology will influence the relative prevalence of CCSVI between patients with MS and healthy individuals or patients with other central nervous system diseases (65).

The ISNVD committee proposed further study of an additional screening method based on color Doppler US quantification (62). A recent study used intravenous contrast media-enhanced US to assess cerebral circulation times (CCTs) in patients with MS and healthy individuals, and to determine whether vascular abnormalities can be detected in MS (66). The results of this study (66) showed that, in comparison to control subjects, patients with MS have a significantly prolonged CCT and more frequently retrograde flow in the IJVs, but the longer CCT in patients with MS was not related to CCSVI. Contrast-enhanced US was proposed as an additional diagnostic modality and research tool that could help identify cerebral venous abnormalities and increase our knowledge of this condition (66).

APPENDIX B: MR IMAGING CCSVI PROTOCOL

In addition to the conventional brain and spinal-cord MR imaging sequences proposed by the Consortium of Multiple Sclerosis Centers consensus guidelines for MR imaging studies in patients with MS (67), additional specialized MR imaging sequences are added to study the vasculature in the neck (Table E1 and Figs E6, E7). On the vascular side, anatomic and flow information are collected.

The following imaging protocols with contrast medium (Table E2) or without contrast medium (Table E3) are shown for a 3-T scanner but can be extended easily to other field strengths such as 1.5 T (Figs E8, E9). The scans proposed are: two-dimensional (2D) TOF MR venography, time-resolved contrast-enhanced three-dimensional (3D) MR angiography and venography, phase-contrast flow data at different levels in the neck, as well as the conventional T2-weighted imaging, fluid-attenuated

inversion recovery (FLAIR), and pre- and postcontrast T1-weighted imaging or magnetization-prepared rapid gradient-echo (MPRAGE) imaging of the brain.

Two-dimensional TOF MR venography scans are used to detect blood flow in arteries and veins (Fig E8). Using a saturation band, any flow toward the head (ie, arterial flow) will be saturated and the flow toward the heart (ie, venous flow) will be highlighted in a velocity-dependent manner. From this sequence, veins are well visualized, and it can be determined if they are patent, occluded, or stenosed. As the data are collected with high resolution, vessel cross-section can also be calculated to evaluate the degree of stenosis.

Three-dimensional contrast enhanced MR angiography and venography can also be used to evaluate vascular abnormalities (Fig E8). The scan uses a T1 reducing contrast agent that passes through all vessels and leads to an increased signal for vessels in T1-weighted scans. From the data, 3D anatomic assessments can be performed to evaluate vessel patency. Atresias, aplasias, truncular malformations, valve issues, and stenoses can be detected.

Two-dimensional phase-contrast MR images are used to assess flow dynamics in the head and neck veins as well as arteries (Fig E9). This information is valuable because it can corroborate and complement the information in the 2D TOF MR venography and 3D contrast-enhanced MR angiography and venography. It is not uncommon to visualize the major veins only later to find that many of the veins have compromised blood flow.

For more conventional imaging, T2-weighted imaging is used to show tissue with long T2 components such as edema, cerebrospinal fluid (CSF), tumors, and lesion pathologic processes. Two-dimensional or 3D FLAIR is used because the images have suppressed CSF signal. FLAIR shows periventricular lesions well without the interference from CSF. Lesion quantity and volume can also be assessed with FLAIR. Eventually, it may be possible to compare lesion volume with blood flow or the subject's physiologic changes over time. T1-weighted imaging is used at two junctures of the scanning protocol to image the head: initially before contrast agent injection and after contrast agent injection. Lesions that enhance after contrast agent administration are considered as acute.

Scanning Procedure

- Initially, register the patient along with his/her height and weight. This plays an important role in flow quantification (tiers 1 and 2);
- Activate appropriate (head, neck, and spine) coils for imaging the region of interest (tiers 1 and 2);
- Make sure to put the pulse trigger on the subject's (left/right) index finger or, for a better flow quantification, cardiac gating can be used (tiers 1 and 2);
- Initially, start imaging the head by using T2, MPRAGE, FLAIR, and T1-weighted imaging

sequences. Make sure to use the head and neck coils (tiers 1 and 2);

- Next, move the table to center at the neck and acquire T2, 3D contrast-enhanced MR angiography and venography, and flow quantification sequences. Make sure to use the head and neck coils. Inject the contrast agent at the fourth or fifth measurement of the 3D contrast-enhanced MR angiography and venography (tier 2);
- The flow quantification plane will be set perpendicular to the IJVs at the C2/C3 and C6/C7 neck levels with a velocity-encoded gradient echo imaging of 50 cm/s (tier 2);
- Next, move the table center back to the head and acquire the data by using the post-gadolinium injection MPRAGE sequence (tier 2).

Reporting the Data

Beyond the standard clinical diagnostic data review by the neuroradiologist, one must also consider the 2D TOF and/or the 3D contrast-enhanced MR angiographic data and the flow data. For the former, one can consider anatomic and vascular abnormalities in various vessels, including the carotid arteries, vertebral arteries, jugular veins, external jugular veins, anterior jugular veins, VVs, deep cervical veins, vertebral plexus, facial veins, and thyroid veins. The CSAs of these vessels can be evaluated at C2/C3 and C5/C6 by using the 3D contrast-enhanced MR angiography and venography or the 2D TOF MR venography data.

Further considerations include the presence of stenoses, truncular venous malformations, and malfunctioning valves. Qualitative evaluation of IJV morphology includes classification into five categories using an ordinal scale: absent (flow not visible), pinpoint, flattened, crescentic, and ellipsoidal, considering each subject's score to be their highest level of morphologic abnormality (68–72). The presence and severity of IJV caliber changes and non-IJV collateral vessels are graded by using a four-point scale (73,74). Another more quantitative criterion that has been used in the recent literature includes the use of a CSA of less than 25 mm² (ie, one third of the CSA for an average IJV diameter of 1 cm assuming a circular shape) at the lower half of the IJV body below C2/C3 to call the vein stenotic and a CSA of less than 12.5 mm² at the C2/C3 level as stenotic (75–77).

The flow can also be reported from the C2/C3 and C6/C7 levels for arteries and veins (75–78). This can include the percentage of IJV flow compared with the arterial flow in that region, the ratio of dominant to subdominant IJV flow, and the presence of no flow, reflux, and circulatory flow. Users should be aware of aliasing and use antialiasing software to process the flow data. The flow data can be presented in terms of integrated flow in milliliters per second, speed in centimeters per second, positive flow in milliliters per second (to show flow toward the brain

and better visualize reflux or circulatory flow), or negative flow in milliliters per second, all throughout the cardiac cycle. Blood flow in the IJVs can be normalized to the total arterial flow at a given location as follows: at the C6/C7 level, total arterial flow includes blood through the common carotid arteries and the vertebral arteries combined, whereas, at the C2/C3 level, total arterial flow includes blood through the internal carotid arteries and the vertebral arteries combined. One such software that is available for use is Signal Processing in Nuclear Magnetic Resonance, or SPIN (75–77).

APPENDIX C: CATHETER VENOGRAPHY CCSVI PROTOCOL

Vascular Access

We recommend the right femoral (or saphenous) vein access for routine assessment and possible consideration of a venography of the IJV and azygous veins. Left femoral vein access may be an option if the screening of additional veins, such as the left iliac vein, is planned.

Angiographic Contrast

Diluted contrast medium allows a clearer visualization of intraluminal structures, whereas nondiluted contrast medium enables a better visualization of the collateral vessels (79). Also, there is no clear consensus on whether the contrast medium should be hand- or pressure-injected. Although hand injection mimics physiologic venous flow, pressure injectors are more accurate, and their use is more reproducible and makes some flow-related analyses quantifiable. Consequently, there are proponents of each approach.

Introducer Sheath, Diagnostic Catheter, and Guide Wires

Use of an 8-F introducer sheath for routine venography is recommended (79). The veins should be selectively cannulated by using a 0.035-inch hydrophilic coated guide wire, and the venograms should be obtained through a 5-F angled diagnostic catheter. Radiographs should be taken at different angles (eg, anteroposterior, lateral, and anterior oblique). In a case of challenging anatomy, other guide wires and catheters may be advantageous.

What Should Be Interpreted as a Pathologic Process

The following lesions should be interpreted as pathologic, and will present with all the following criteria:

- Lesion detected in any part of IJV uni- or bilaterally (also comprises lesions of the brachiocephalic veins);
or
Lesion of the arch of the azygos vein and/or ascending azygos vein;
or

Lesion of the hemiazygous or accessory hemiazygous vein if these veins constitute primary outflow route from the spinal cord;

- At least 50% stenosis of the vein, if compared with diameter of adjacent segment of the vein; also comprises severe hypoplasia, complete agenesis, and secondary occlusion of the vein (eg, thrombotic; (Figs E10, E11);
or
- Intraluminal structures, such as webs, septa, or membranes, which are associated with at least one additional sign of impaired outflow:
 - No outflow of contrast agent from the vein,
 - Outflow of contrast agent slowed down, ie, retained in examined vein for longer than one cardiac cycle,
 - Backward flow of injected contrast agent (using low-pressure and low-volume injection),
 - Outflow of injected contrast agent through collaterals instead of the main vein.
- Such an abnormality should be demonstrated by using hand injection of the contrast agent or the use of a low-pressure automatic injector.

Debatable Venographic Abnormalities

Debatable venographic abnormalities include any of the following findings:

- Lesions of the distal part of the azygos vein, hemiazygous vein, or their tributaries;
- Lesions of the hemiazygous or accessory hemiazygous vein if these veins are not dominant;
- Abnormalities of the VVs;
- Lesions revealed by using a high-pressure injector;
- Stenosis less than 50% with no other sign of compromised outflow;
- Intraluminal structures not associated with the signs of compromised outflow;
- Stenosis or intraluminal structures associated with prestenotic dilation of the vein but no other signs of compromised outflow;
- Phasic stenosis, ie, a narrowing that is not visible permanently but only during a fraction of the cardiac or respiratory cycle;
- Stenosis visible only by using inflation of compliant angioplastic balloon or on intravascular US, with no additional venographic signs of compromised outflow.

APPENDIX D: INTRAVASCULAR US CCSVI PROTOCOL

Intravascular US is generally used in adjunct to catheter venography (CV). It may, in limited circumstances, be a “stand-alone” diagnostic and therapeutic tool in the presence of contraindications to the administration of contrast media (ie, in patients with estimated glomerular filtration rate < 45–60 mL/min, especially if

complicated by diabetes mellitus or previous life-threatening allergic reactions to contrast agents).

Intravascular US is indicated in patients with suspected intraluminal venous pathologic conditions. As CCSVI is frequently associated with valvular malformations and other intraluminal causes of obstruction, such as webs, membranes, duplications, and septa, intravascular US is indicated in the diagnostic evaluation of suspected outflow obstructions of the cerebrospinal venous circulation.

Technical and cognitive expertise with intravascular US is essential for its proper use. Observation and learning in a center where intravascular US is used routinely in venous disease is advisable before independently performing such procedures.

Description of Intravascular US Procedure

Before advancing the intravascular US device through the right atrium, it is strongly advised that a sheath be placed across the right atrium. The 0.014–0.018-inch guide wires used to track the intravascular US device are so thin that they may buckle into the right atrium or ventricle and cause ventricular and atrial ectopic rhythms or other tachyarrhythmias.

When both examinations are performed during a single treatment, intravascular US should follow CV. CV provides a topographic analysis of the venous anatomy and pathology as well as estimations of flow. At the completion of venography, a 0.014-inch wire is left at the highest level of intravascular US interrogation and the diagnostic catheter is exchanged for the intravascular US catheter wire at its furthest reach in the vein of interest. With the active unit, the device is withdrawn by hand in one smooth motion from the IJV through the brachiocephalic vein. Use of the motorized withdrawal unit is discouraged as it is too slow to be practical in such a long vessel. The device is then advanced back into the IJV stopping as needed for further interrogation of areas of interest. If dural sinus abnormalities are suspected, intravascular US can also be used in the sinus as a separate examination.

In some cases of very large veins, the intravascular US field of interest may be insufficient to visualize the entire vein, especially when the intravascular US image lies eccentrically along one wall of the vein. Maneuvers to center the intravascular US image rely on advancing the intravascular US catheter away from the wall by placing the wire into a branch until the wire and intravascular US catheter are displaced away from the wall. With the patient changing head position, it can be determined if a stenosis is a true stenosis or an effect of a compression (especially at J2 level). Another alternative would be to switch to a catheter with lower frequency.

The accumulated data are then viewed in axial and longitudinal views, looking for echogenic intraluminal abnormalities such as immobile valves, unileaflet valves,

adhesions, thickening, and thrombus. Webs and septations are sometimes better visualized on the longitudinal view. CSA measurements are taken at the sites of potential angioplasty. Cross-sectional calculations by intravascular US are superior to fluoroscopic estimations of diameters. Comparisons of normal vein size versus stenotic areas can also be calculated more accurately.

Because many abnormalities are diagnosed predominantly by intravascular US and because most complications of angioplasty are mural and intraluminal in nature, intravascular US should be repeated in every vessel (**Fig E12**). At completion of the treatment of any vein, intravascular US is removed and CV proceeds into the next vessel, again followed by intravascular US.

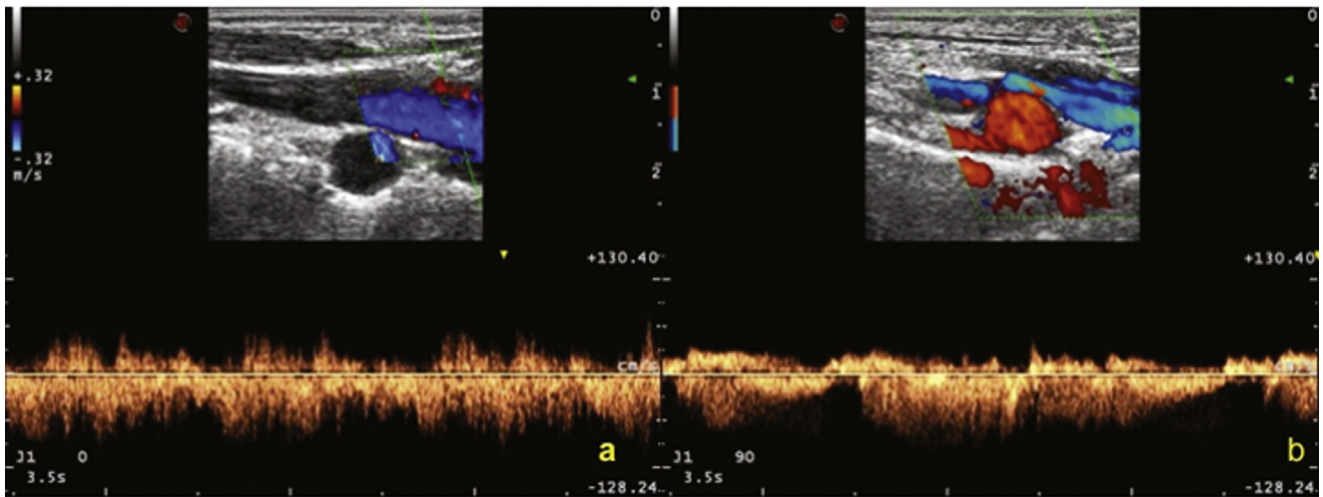


Figure E1. Bidirectional flow in the IJV seen in longitudinal view assessed by a Doppler spectral waveform. The duration of the reverse flow more than 1 second is well apparent in supine (**a**) or in sitting position (**b**), fulfilling the first VH criterion.

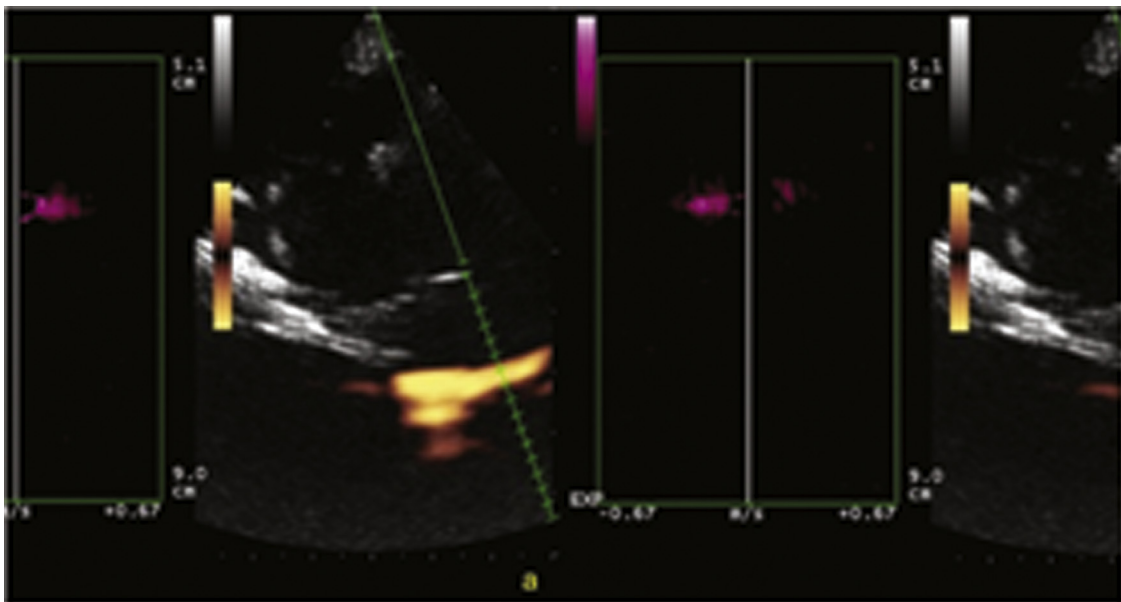


Figure E2. An example of reflux: the blood flow at the level of the superior petrosal sinus shows opposite directions between the two phases of respiration: (**a**) during inspiration, the flow is directed toward the frontal side, but during expiration (**b**), the flow has the opposite direction toward the occipital side. This finding shows the presence of reversed blood flow within the examined vessel: the second VH criterion.

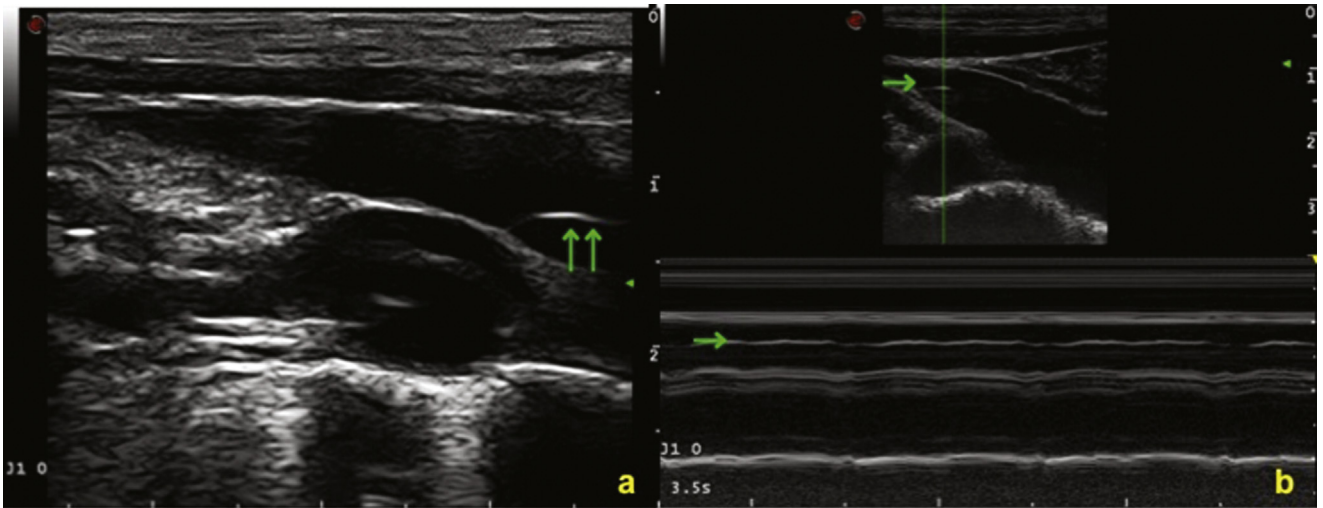


Figure E3. B-mode evaluation of the IJV at J1 level (longitudinal view): **(a)** the arrows indicate a septum in the middle of the vessel lumen. **(b)** The immobility of such a septum demonstrated in M-mode (arrow), fulfilling the third VH criterion.

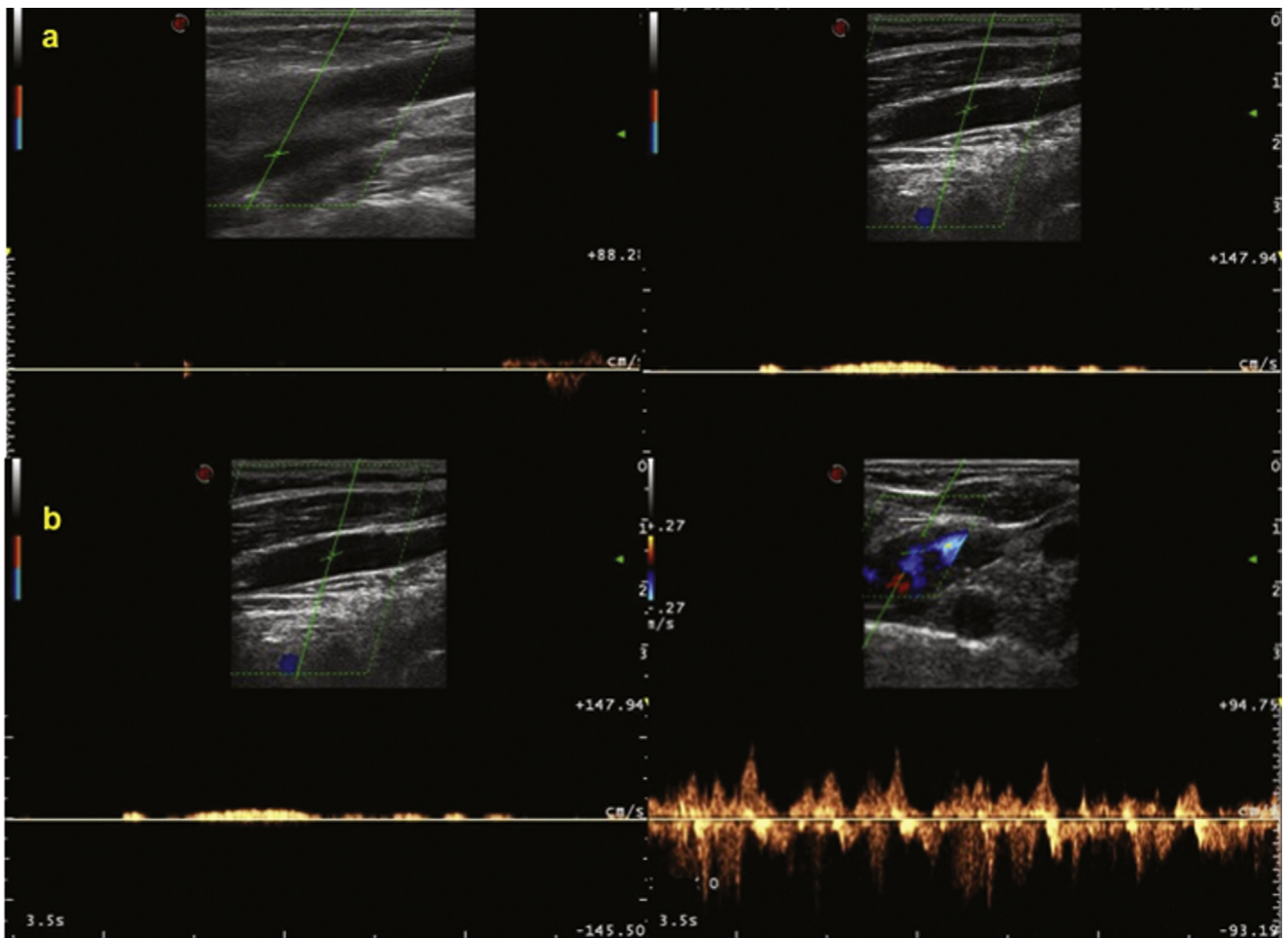


Figure E4. **(a)** An example of absence of detectable flow in longitudinal scan of an IJV in supine (left) and sitting (right) postures. The PRF has to be settled at no more than 1.2 kHz. This finding is a reflection of positive VH criterion 4a. **(b)** In this case, the absence of detectable flow (left) is coupled with the presence of bidirectional flow (right), fulfilling VH criterion 4b.

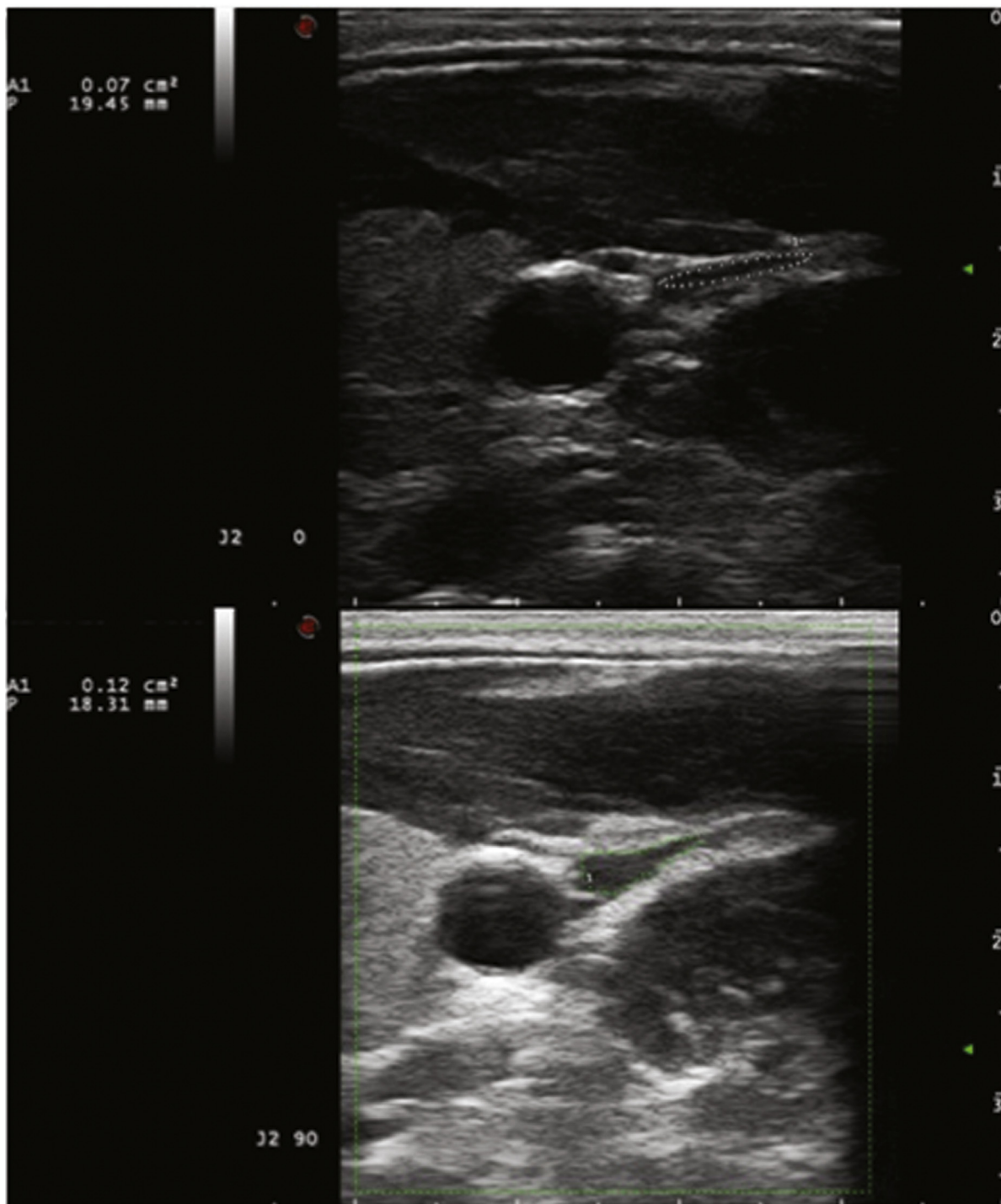


Figure E5. Upper: example of the CSA measurement of the IJV in the supine position (VH criterion 5). Lower: Example of CSA measurement of the IJV in sitting position. Δ CSA is negative, as it is greater in the sitting than in the supine position.

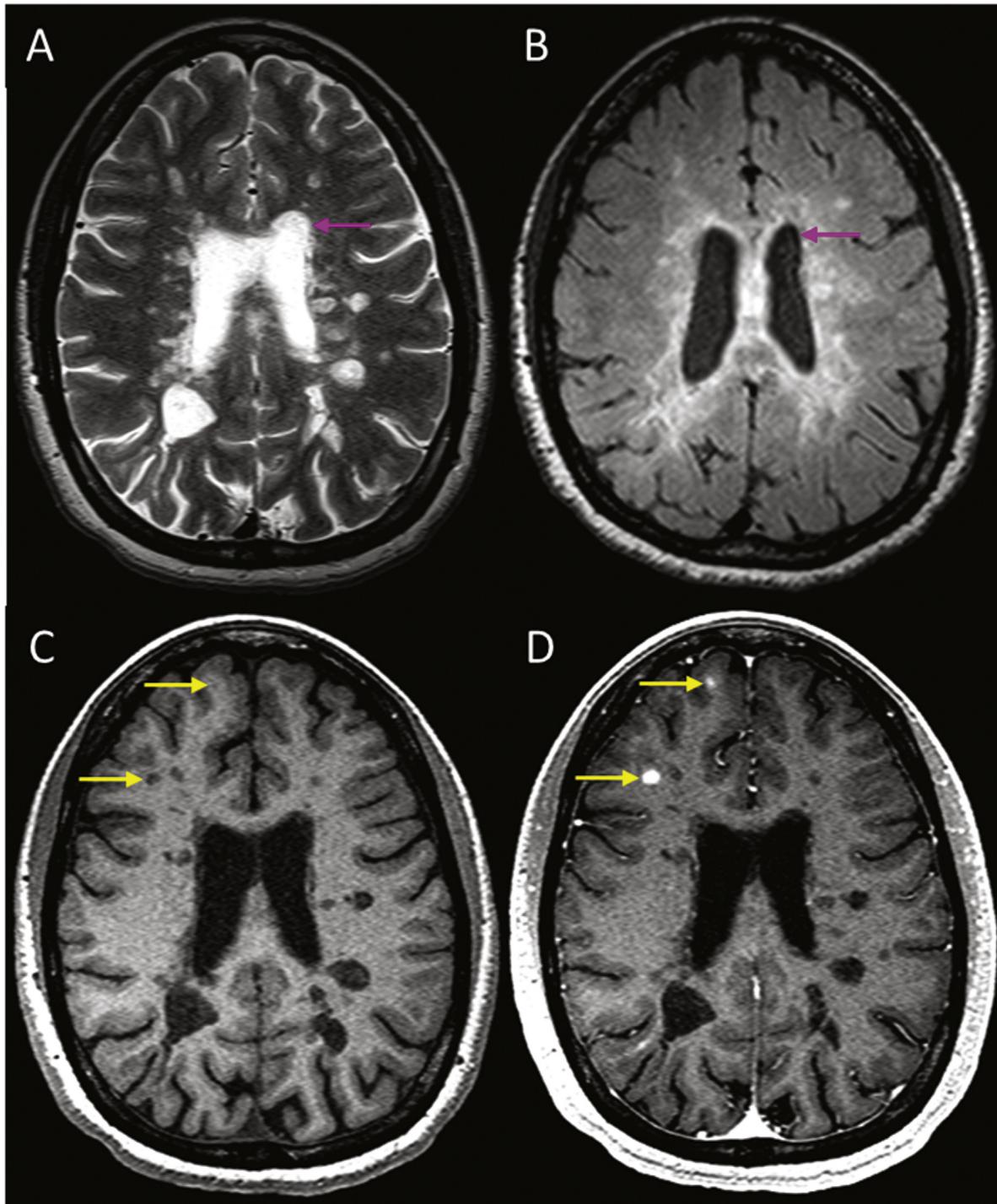


Figure E6. Conventional MR scans show the appearance of MS lesions in the brain. (a) Axial T2-weighted imaging and (b) FLAIR show hyperintense lesions within the white matter. The CSF signal appears bright on T2-weighted imaging (arrow, a), but, on FLAIR imaging, the CSF signal intensity is greatly reduced, allowing for the clear visualization of periventricular lesions (arrow, b). (c) Precontrast T1-weighted imaging is another modality in which MS lesions are observed (arrows), and a major benefit of having a T1-reducing contrast agent allows for (d) postcontrast T1-weighted imaging in which some MS lesions may become enhanced (arrows). This enhancement indicates that the blood mixed with contrast agent is able to enter the parenchyma, meaning that the blood–brain barrier is disrupted.

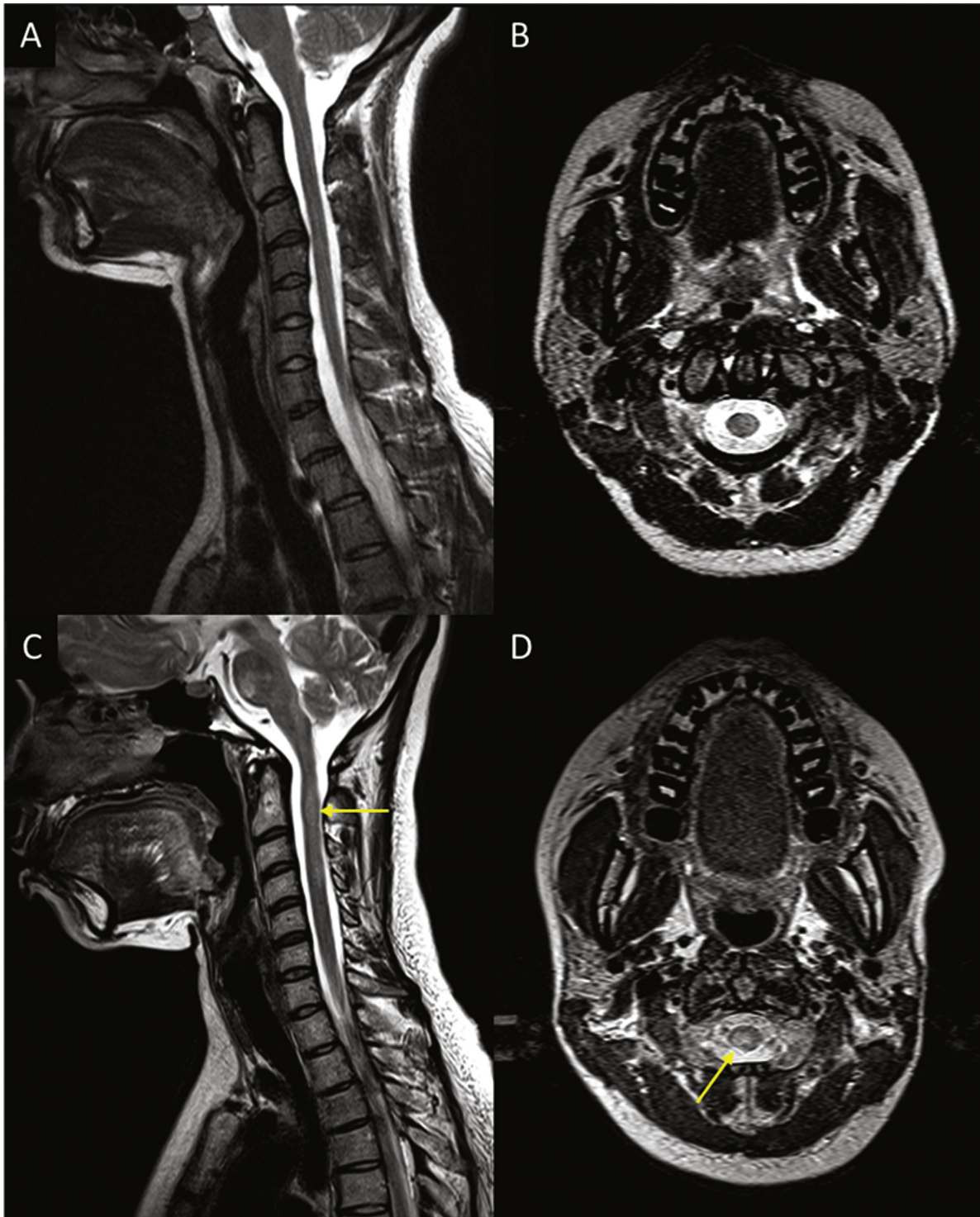


Figure E7. Spine imaging: T2-weighted imaging covering the cervical spinal cord of a healthy control subject (a,b) and a patient with MS (c,d) with spinal lesions. A sagittal T2-weighted slice (a) shows healthy white matter with uniform signal through the cervical spinal cord, and a separate axial T2-weighted slice (b) confirms this appearance. In the patient with MS, hyperintense lesions are noticeable (arrow, c,d) in the sagittal (c) and axial (d) images.

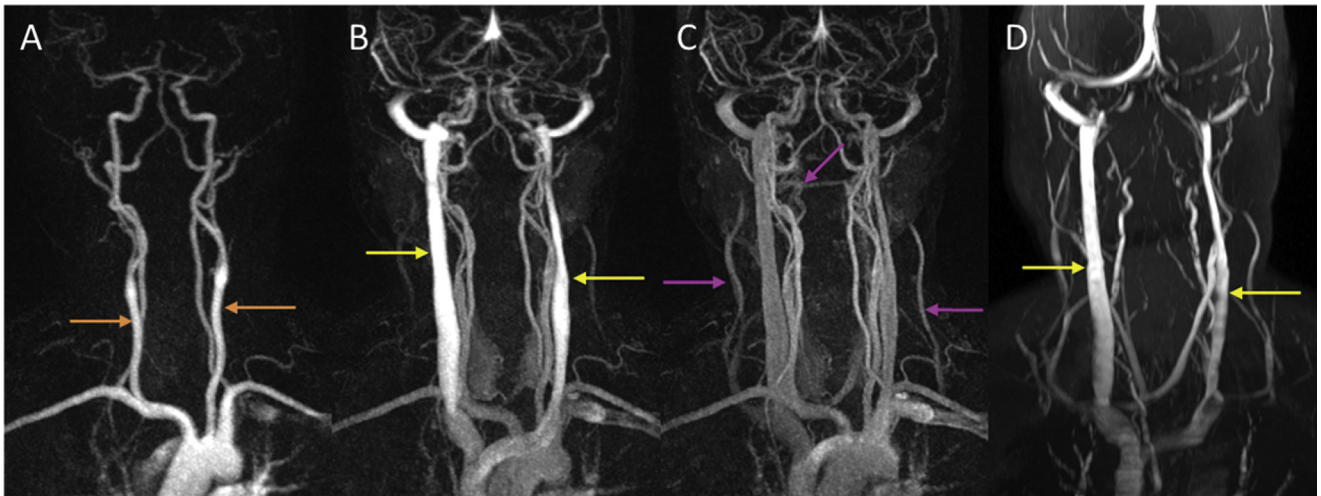


Figure E8. Vasculature of the head and neck. Arteries and veins can be visualized with and without the use of an exogenous contrast agent as represented here in coronal projections of two modalities. **(a–c)** Dynamic contrast-enhanced MR angiography has temporal resolution capable of imaging arterial **(a)**, early venous **(b)**, and late venous **(c)** phases. This allows for the clear visualization of the arterial system, including the common carotid arteries (arrows, **a**), as well as the venous system, including the IJVs (arrows, **b**) and late-enhancing collateral vessels (arrows, **c**). **(d)** With a tracking caudal saturation band suppressing signal within the arterial system, 2D TOF MR venography allows for the visualization of the venous system as a whole, including the IJVs (arrows, **d**).

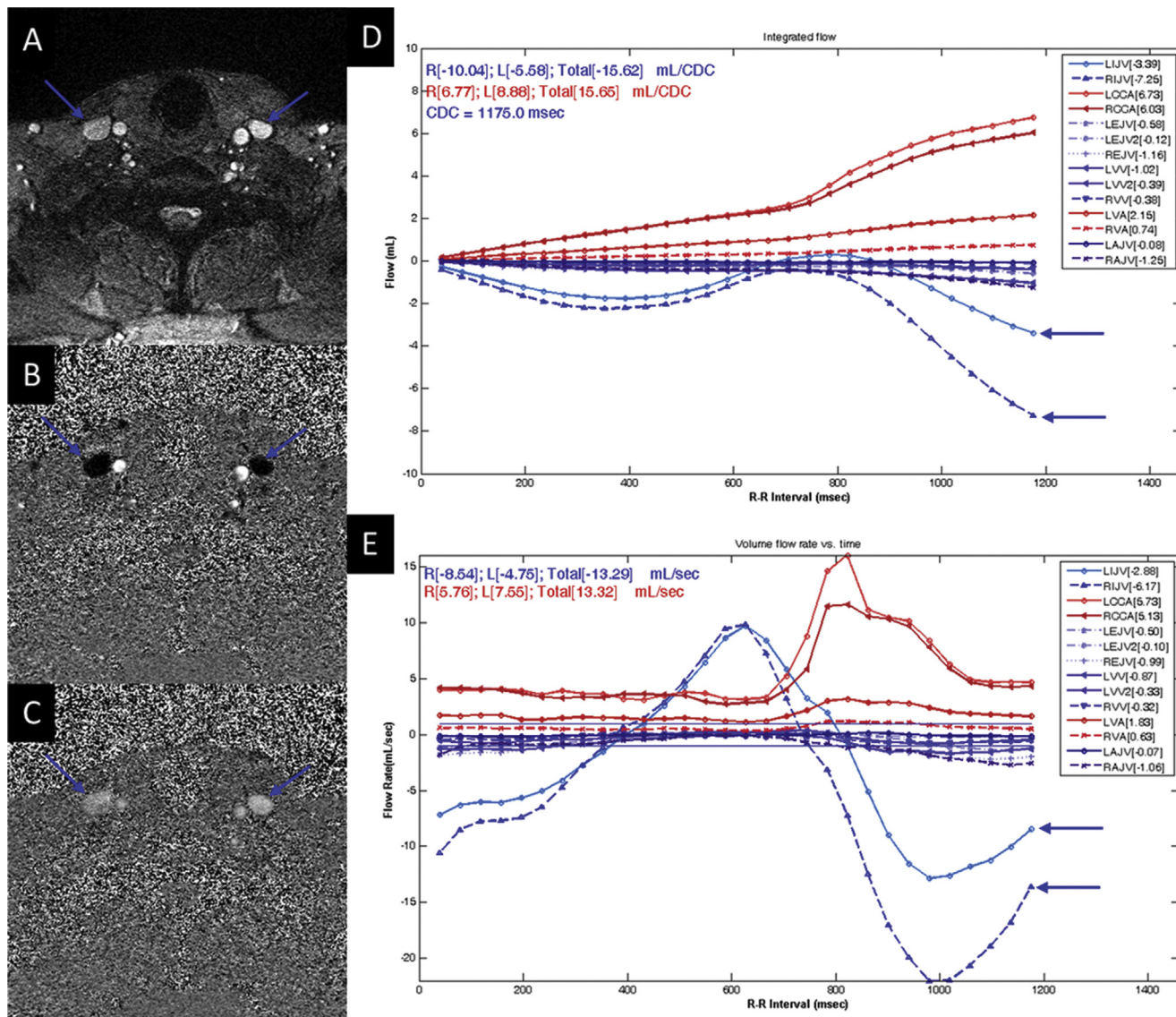


Figure E9. Quantification of blood flow: 2D phase-contrast MR imaging is a method that quantifies velocity passing through the acquisition slice as shown here at a slice positioned perpendicular to the major vessels of the neck between the sixth and seventh cervical vertebrae. (a) An axial magnitude image shows clear visualization of the vessels with blood flow in the neck, eg, IJVs (arrows, a). (b,c) Axial-phase images show signal intensity directly proportional to the velocity of flow through the slice. A reversal of flow is shown in the IJVs when the signal intensity changes from dark (arrows, b), meaning blood flow toward the heart, to bright (arrows, c), which indicates blood flow toward the brain. (d,e) When a region of interest is defined containing a vessel, the average velocity can be calculated from the phase image and then multiplied by the area, giving flow volume (d) and rate (e). Typically, approximately 20–30 time points are collected throughout the cardiac cycle, which are then plotted as a function of time. Consider, for, instance the IJVs (arrows, d,e). From the phase images, a bright signal indicates positive plotted values, and dark signal indicates negative plotted values. Notice that the IJV flow volume begins to show a positive acceleration in the integrated flow plot, and the flow rate values change from negative to positive between approximately 400 and 800 ms, indicating reflux of both of these jugular veins.

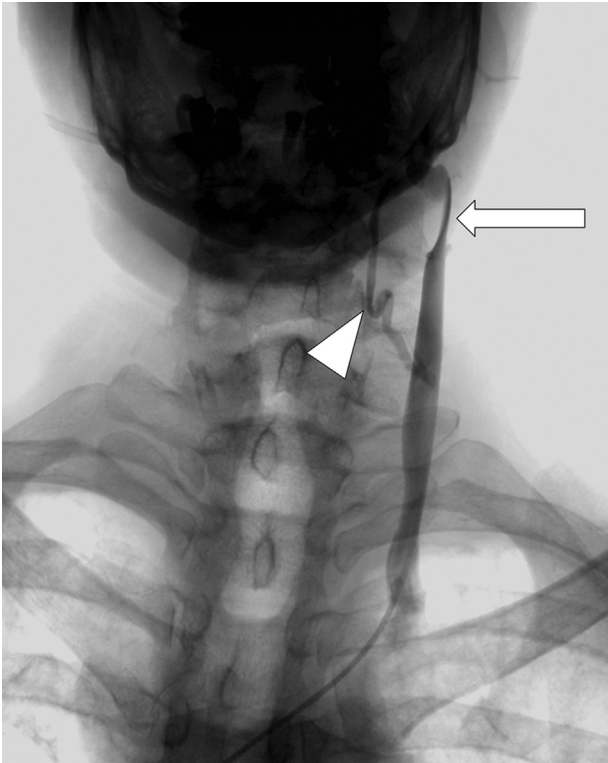


Figure E10. Stenosis in the upper part of the left IJV (arrow) with outflow of injected contrast agent through collateral network (arrowhead).

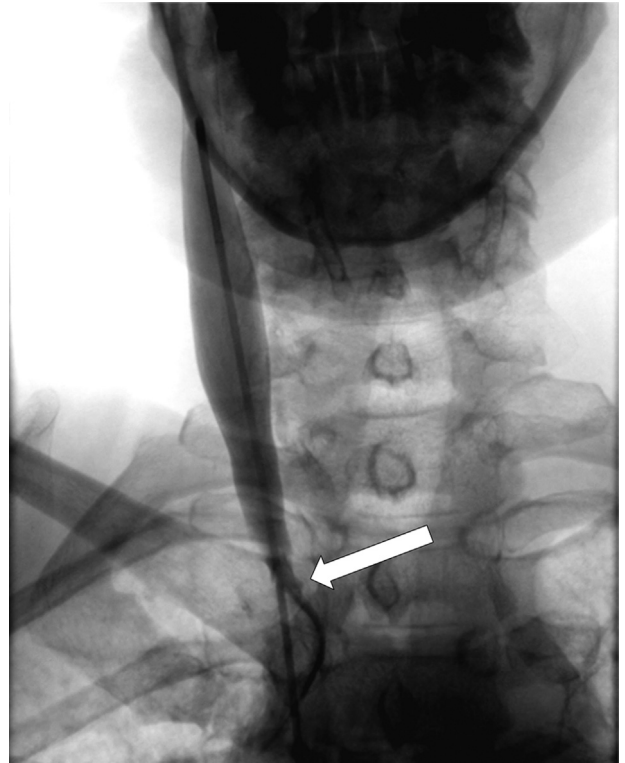


Figure E11. Severe stenosis (arrow) of the right IJV at the level of the jugular valve.

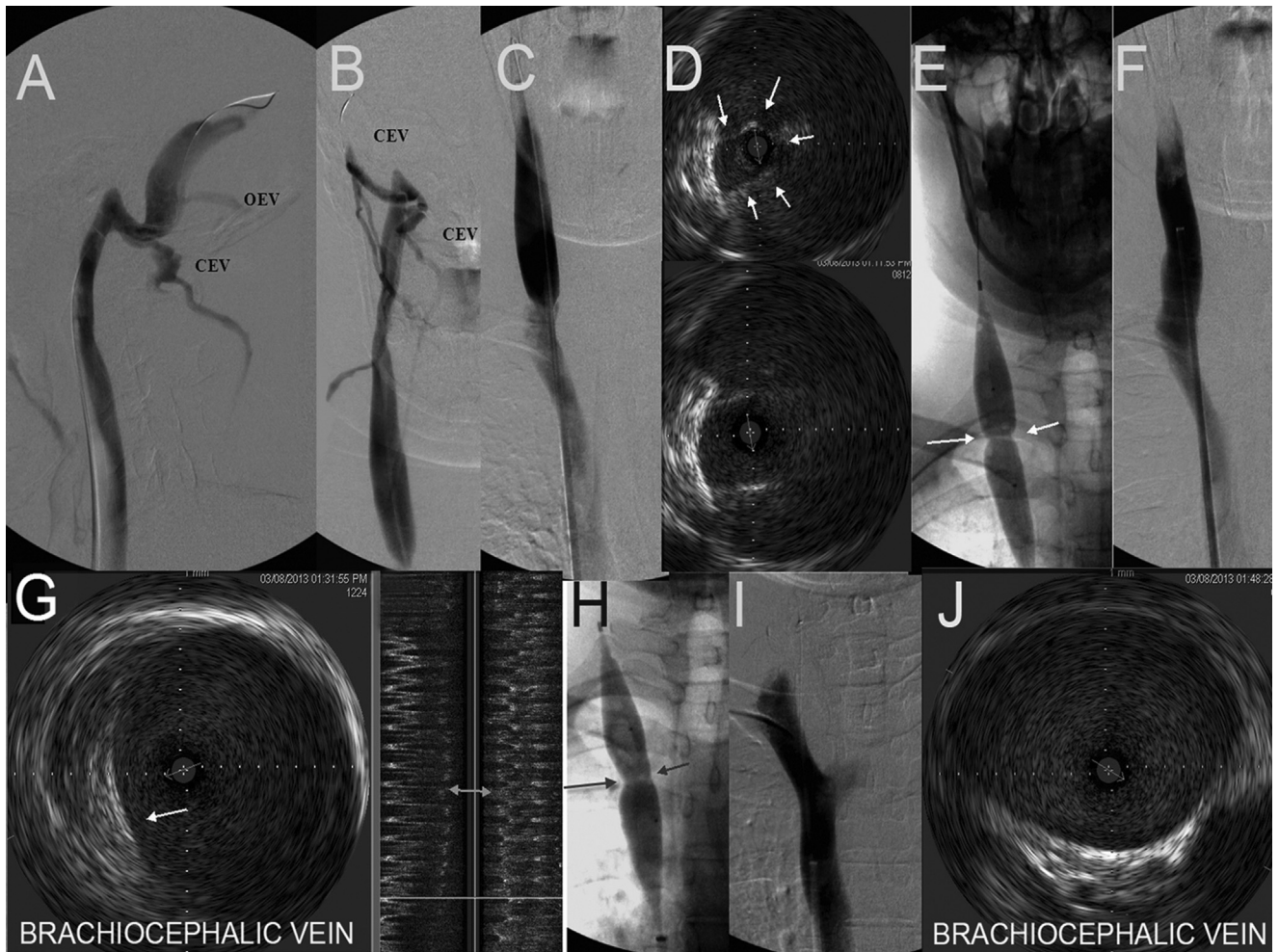


Figure E12. Images from a 29-year-old man who presented with a recent onset of relapsing-remitting MS. Symptoms included cognitive difficulties, short-term memory lapses, numbness, urinary retention and incontinence, and imbalance. CV and intravascular US were performed. **(a,b)** Frontal and lateral dural sinus venography showed that there was reflux into the condylar emissary vein and the occipital emissary vein. **(c)** Frontal venography of the IJV showed high-grade stenosis that can easily be missed on venography. **(d)** Intravascular US reveals a high-grade stenosis (> 80%) of thickened internal jugular valves (outlined by arrows). **(e)** A 20-mm high-pressure balloon was inflated to 14 atm to open the valvular stenosis (arrows). **(f)** After angioplasty appears to have opened the obstruction, **(g)** intravascular US shows that there is a second immobile valve in the brachiocephalic vein (arrow). Longitudinal view clarifies the degree of stenosis (double arrowhead). **(h)** An 18-mm high-pressure balloon inflated to 16 atm opened this immobile valve (arrows), and **(i)** venography shows improved luminal diameter and better flow. **(j)** Intravascular US of the brachiocephalic vein shows that the valve is now open.

Table E1 . Standard Brain and Spinal Cord MR Imaging Protocol for Patients with Multiple Sclerosis According to the Consortium of Multiple Sclerosis Center Consensus Guidelines for MR Studies (67)

Sequence	Approximate Time Interval	
	3-T MR Imaging	1.5-T MR Imaging
Three-plane scout of brain (localizer)	0:15	0:10
Axial T2/proton density, head	2:50	4:30
Axial T2 fast FLAIR	2:30	4:30
Axial T1 head 3D before gadolinium	4:00	4:20
Inject gadolinium (no wait time)	0:00	0:00
Axial T1 head 3D after gadolinium	4:00	4:20
Three-plane scout of cervical spine (localizer)	0:20	0:15
Sagittal T2/proton density, cervical spine	2:10	3:50
Sagittal T1 cervical spine after gadolinium	2:40	5:00
Select axial T2 cervical spine through lesions	1:50*	2:20*
Select axial T1 cervical spine after gadolinium through lesions	1:50*	2:40*
Total time	20:45 (24:25*)	26:55 (31:55*)

* = optional, FLAIR = fluid-attenuated inversion recovery.

Table E2. Tier 1 Protocol for Studying CCSVI without Contrast Agent Administration on 3-T MR Imaging

Detail	Head (Center at Orbital Ridge)			Neck (Center at Chin)				
	1	2/9	3	4	5/10	6	7	8
Sequence order								
Sequence type	T2/PD	T1 MPRAGE	3D FLAIR	T2/PD cervical spine	T1 cervical spine	T2 cervical spine through lesions	2D TOF MR venography (neck)	Flow quantification (jugular)
Sequence	tse	tfl	tse_vfl	tse	tse	tse	fl_tof	fl_fq_retro
Orientation	Axial	Axial	Sagittal	Sagittal	Sagittal	Axial	Axial	Axial
TR (ms)	3,000	1,750	6,000	3,200	2,140	4,160	29	95.25
TE (ms)	12,105	2.98	397	22,100	10	94	5.02	10
TI (ms)	–	900	2200	–	899	–	–	–
FA (°)	150	9	–	150	160	130	60	20
FOV (mm ²)	256 × 192	256 × 256	256 × 256	256 × 192	256 × 256	256 × 256	320 × 256	256 × 256
Matrix size	256 × 256	512 × 256	256 × 256	256 × 256	256 × 256	256 × 256	512 × 256	448 × 448
Nz/TH (mm)	46/3	192/1	160/1	17/3	17/3	19/3	128/3	1/2.5
Voxel size (mm ³)	1 × 1 × 3	0.5 × 1 × 1	1 × 1 × 1	1 × 1 × 3	1 × 1 × 3	1 × 1 × 3	0.6 × 1.3 × 3	0.6 × 0.6 × 2.5
Average/meas.	1	1	1	2/1	1/1	3/1	1	1
Concatenations	4	1	1	1	2	1	–	–
Phase oversmpl (%)	0	0	0	0	100	0	–	0
Dist. factor (%)	0	0	0	0	0	0	–25.0	20
Phase enc. dir	R>>L	R>>L	A>>P	A>>P	H>>F	A>>P	A>>P	A>>P
iPAT	2/31	2/24	2/24	2/32	2/27	2/32	2/24	2/24
BW (Hz/pixel)	181	180	781	142	230	250	217	192
Flow comp	Slice	No	No	Read	No	Slice	Yes	No
Phase partial Fourier	Off	Off	Allowed	Off	Off	Off	Off	Off
Slice partial Fourier	Off	Off	7/8	Off	Off	Off	Off	Off
Flow mode/direction	–	–	–	–	–	–	–	Single dir./through plane
Venc. (cm/s)	–	–	–	–	–	–	–	50
1st signal/mode	–	–	–	–	–	–	–	Pulse/retro
Special saturation	–	–	–	–	–	–	Tracking F	–
Presaturation	–	–	–	–	–	–	Gap10 mm; TH 40 mm	–
Echo spacing (ms)	11.7	7.6	3.32	11.1	9.94	11.8	–	–
Turbo factor	7	–	141	5	9	15	–	–
Echo trains per slice	16	–	1	20	30	9	–	–
Coils	Head	Head	Head/Neck	Head/Neck/SP1,2	Head/Neck/SP1,2	Head/Neck/SP1,2	Head/Neck/SP1,2	Head/Neck/SP1,2
Time	03:26	04:03	05:20	02:13	02:14	1:58*	06:57	01:42 (×2)
Total time	–	–	–	–	–	–	–	27:37 (29:35)*

Recommendations: (i) follow the sequence order, (ii) put a pulse trigger on the patient's index finger, and (iii) flow quantification will be done perpendicular to the internal jugular veins at the C2/C3 and C6/C7 neck levels with a venc of 50cm/s. * = optional, A = anterior, BW = bandwidth, C = cervical, CCSVI = chronic cerebrospinal venous insufficiency, dist. factor = fraction of the slice thickness left between slices for 2D imaging methods, FA = flip angle, FLAIR = fluid-attenuated inversion recovery, FOV = field of view, iPAT = increase in speed factor for parallel imaging, L = left, MPRAGE = magnetization-prepared rapid acquisition gradient-echo, Nz/TH = number of slices/slice thickness, phase enc. dir = phase encoding direction, phase oversmpl = percentage of extra phase encoding lines collected relative to what is required, P = posterior, PD = proton density, R = right, TE = echo time, tfl = turbo flash, 3D = three-dimensional, TI = inversion time, TR = repetition time, tse = turbo spin-echo, TOF = time of flight, venc. = velocity-encoded gradient echo imaging.

Table E3 . Tier 2 Protocol for Studying CCSVI with Contrast Medium Administration on 3-T MR Imaging

Detail	Head (Center at Orbital Ridge)				Neck (Center at Chin)					
	1	2/9	3	4	5/10	6	7	8	11	
Sequence order										
Sequence type	T1 MPRAGE		T2/PD		T1 cervical spine pre-/postcontrast	T2 cervical spine through lesions	3D TWIST inject contrast at the start of 5th measurement	Flow quantification (jugular)	T1 cervical spine through lesions	
Sequence	tse	tfl	tse_vfl	tse	tse	tse	twist	fl_fq_retro	tse	
Orientation	Axial	Axial	Sagittal	Sagittal	Sagittal	Axial	Coronal	Axial	Axial	
TR (ms)	3,000	1,750	6,000	3,200	2,140	4,160	3.31	95.25	2,000	
TE (ms)	12,105	2.98	397	22,100	10	94	1.25	10	9.9	
TI (ms)	–	900	2,200	–	899	–	–	–	–	
FA (°)	150	9	–	150	160	130	18	20	160	
FOV (mm ²)	256 × 192	256 × 256	256 × 256	256 × 192	256 × 256	256 × 256	340 × 255	256 × 256	256 × 256	
Matrix size	256 × 256	512 × 256	256 × 256	256 × 256	256 × 256	256 × 256	384 × 384	448 × 448	256 × 256	
Nz/TH (mm)	46/3	192/1	160/1	17/3	17/3	19/3	96/0.9	1/2.5	19/3	
Voxel size (mm ³)	1 × 1 × 3	0.5 × 1 × 1	1 × 1 × 1	1 × 1 × 3	1 × 1 × 3	1 × 1 × 3	0.9 × 0.9 × 0.9	0.6 × 0.6 × 2.5	1 × 1 × 3	
Average/meas.	1	1	1	2/1	1/1	3/1	1/20	1	2/1	
Concatenations	4	1	1	1	2	1	–	–	3	
Phase oversmpl (%)	0	0	0	0	100	0	0	0	0	
Dist. factor (%)	0	0	0	0	0	0	–	20	0	
Phase enc. dir	R>>L	R>>L	A>>P	A>>P	H>>F	A>>P	R>>L	A>>P	A>>P	
iPAT	2/31	2/24	2/24	2/32	2/27	2/32	2/24	2/24	2/32	
BW (Hz/pixel)	181	180	781	142	230	250	650	192	230	
Flow comp	Slice	No	No	Read	No	Slice	–	No	No	
Phase partial Fourier	Off	Off	Allowed	Off	Off	Off	6/8	Off	Off	
Slice partial Fourier	Off	Off	7/8	Off	Off	Off	6/8	Off	Off	
Flow mode/direction	–	–	–	–	–	–	–	Single dir./ through plane		
Venc. (cm/s)	–	–	–	–	–	–	–	50	–	
1st signal/mode	–	–	–	–	–	–	–	Pulse/retro	–	
Echo spacing (ms)	11.7	7.6	3.32	11.1	9.94	11.8	–	–	9.94	
Turbo factor	7	–	141	5	9	15	–	–	9	
Echo trains per slice	16	–	1	20	30	9	–	–	15	
Coils	Head	Head	Head/neck	Head/neck/SP1,2	Head/neck/SP1,2	Head/neck/SP1,2	Head/neck/SP1,2	Head/neck/SP1,2	Head/neck/SP1,2	
Time	03:26	04:03 (×2)	05:20	02:13	02:14 (×2)	1:58*	02:26	01:42 (×2)	3:08*	
Total time	–	–	–	–	–	–	–	–	29:21 (34:27)*	

Recommendations: (i) follow the sequence order, (ii) put a pulse trigger on the patient's index finger, and (iii) inject remaining dose of contrast medium at the fifth measurement. * = optional, A = anterior, BW = bandwidth, C = cervical, CCSVI = chronic cerebrospinal venous insufficiency, dist. factor = fraction of the slice thickness left between slices for 2D imaging methods, FA = flip angle, FLAIR = fluid-attenuated inversion recovery, FOV = field of view, iPAT = increase in speed factor for parallel imaging, L = left, MPRAGE = magnetization-prepared rapid acquisition gradient-echo, Nz/TH = number of slices/slice thickness, phase enc. dir = phase encoding direction, phase oversmpl = percentage of extra phase encoding lines collected relative to what is required, P = posterior, PD = proton density, R = right, TE = echo time, tfl = turbo flash, 3D = three-dimensional, TI = inversion time, TR = repetition time, tse = turbo spin-echo, TOF = time of flight, venc. = velocity-encoded gradient echo imaging.