Diagnostic accuracy of current sonographic criteria for the detection of outflow abnormalities in the internal jugular veins

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Abstract

Objectives: This study was aimed at evaluation of the diagnostic value of Doppler sonography for the assessment of abnormalities in the internal jugular veins (IJVs).

Method: A number of 116 IJVs were assessed in 58 patients with associated multiple sclerosis. Findings of Doppler sonography were compared with results of the reference test: catheter venography.

Results: At least one positive extracranial sonographic criterion suggesting venous abnormality was found in 92.2% of the assessed veins. Yet, sensitivity, specificity, positive and negative predictive values of sonography were low: 93.4%, 12.0%, 79.4% and 33.3% for at least one positive criterion, and for at least two positive criteria: 29.3%, 75.0%, 81.8% and 21.7%, respectively.

Conclusions: Our research has shown that currently used extracranial sonographic criteria for the detection of obstructive venous abnormalities in the IJVs are of limited diagnostic value. For the time being, diagnosis of this vascular pathology should be given using catheter venography.

Keywords: Doppler ultrasonound; phlebography; venous malformation

Introduction

The so-called chronic cerebrospinal venous insufficiency (CCSVI), venous pathology that is characterized by stenoses of extracranial and extraspinal veins draining the brain and spinal cord, primarily the internal jugular veins (IJVs) and the azygous vein, associated with opening of collateral outflow routes and insufficient cerebral venous drainage and connection of this vascular abnormality with multiple sclerosis (MS), is being hotly debated within the scientific community. The hypothetical role for venous blockages in the pathogenesis of MS is not necessarily in contrast to the currently accepted autoimmune model of this disease, since it is known, for example, that pathological venous outflows may trigger inflammatory reaction in other vascular territories. For the time being, the existence of venous abnormalities in MS patients is questioned by only a few researches. Still, prevalence of these vascular lesions is very differently reported. This study was aimed at the evaluation of diagnostic value of Doppler sonography for the assessment of abnormalities in the IJVs.

Methods

There were assessed 58 patients with clinically defined MS: 40 women and 18 men. The patients were aged 22–69 years with a median age of 50 years. This survey was the part of the clinical trial on diagnostics for CCSVI (Doppler sonography, magnetic resonance venography, catheter venography and plethysmography). The study was approved by the Bioethical Committee of the Regional Silesian Board of Physicians in Katowice, Poland (approval...
no. 20/2011). The study has been registered at ClinicalTrials.gov; identifier: NCT01425554. All patients provided their written consent to undergo the procedures and diagnostic tests.

Catheter venography

Catheter venography, which actually was the first part of endovascular procedure in a case of detection of vascular pathology, was performed under mild sedation and local anaesthesia. Venographic examination of the veins was focused on the assessment of outflow abnormalities. Diluted (1:1) iodine-containing contrast, ioxiflusal (Visipaque®), Amersham Health AS, Norway was used, since in our opinion more concentrated dye can overshadow intraluminal defects.

Right femoral access was the preferred one and only in a case of unsuccessful catheterization of right femoral vein the left femoral access was used. We used the following angiographic catheters, depending on local anatomic conditions: Judkins Right (Balton, Poland); Imager II™ (Boston Scientific, USA); VERT Beacon® Tip Torcon NB® Advantage Catheter (Cook Medical Inc., USA) and the following guidewires: 0.035 inch J-tip B.Braun Guidewire (B.Braun, Germany); 0.035 inch angle-tip hydrophilic Glidewire® (Terumo, Japan); 0.018 inch Hi-Torque Steelcore (Abbott Vascular, USA) and 0.018 inch V-18™ Peripheral Guidewire (Boston Scientific).

Contrast was injected with hand, using low pressure. It was injected at different levels of the assessed veins and the radiograms were taken at different angles. Routinely, contrast was injected at the level of the jugular foramen, at the level of junction with facial vein, slightly cranially from the valve in the junction with brachiocephalic vein and sometimes, in doubtful cases, also caudally from this valve. Usually, each injection consisted of approximately 5 mL of diluted contrast. During the injection, the position of the tip of catheter inside or in proximity to a tributary was avoided, since it could produce a false picture of reflux via 'collaterals'. Similarly, too high pressure during the injection can – in our opinion – provoke the outflow of contrast towards intracranial sinuses or vertebral veins (VV), which may inaccurately be interpreted as a backward flow.

Similar to the generally accepted venographic signs of impaired venous outflow in the other veins (like the iliac or axillary vein), the following venographic flow patterns were regarded as abnormal:

- No outflow through the vein;
- Venous outflow slowed down, i.e. a retention of injected contrast in the examined vein longer that one cardiac cycle;
- Reversed flow direction (reflux);
- Outflow through collaterals;
- Intraluminal structures (webs, septa or membranes), hypoplasia or narrowing of the vein compromising outflow, i.e. incurring the retention of injected contrast, reflux or collateral outflow;
- Prestenotic dilation of the vein associated with slowed down flow or reflux;
- Complete occlusion or agenesis of the vein.

Importantly, venous valves in the junction of IJV with brachiocephalic vein were recognized as pathological only if such a valve compromised the outflow in a similar way as other intraluminal structures.

Sonographic examination

Imaging and assessment of the IJVs using colour Doppler sonography was conducted with ultrasound machine GE LOGIQ-e with an 8 MHz linear probe. The probe applied minimal pressure to the skin to prevent undesired compression of the examined veins: the IJVs and VVs. We did not examine intracranial veins, since a special sonographic machine with dedicated software is needed to evaluate the flow in these veins properly. Examinations were performed with patients in the supine and sitting positions. IJVs were evaluated in three locations:

- In the valve area (junction with the brachiocephalic vein) – (J1);
- In the middle part of the vein – (J2);
- In the upper part of the vein (cranially from junction with the facial vein)–(J3).

The following parameters were evaluated in each of these locations and repeated in the supine and sitting positions:

- Flow direction (towards heart, reversed, bidirectional);
- Presence of reflux (flow towards brain) longer than 0.8 seconds;
- Absence of flow;
- Peak flow velocity;
- Presence of intraluminal defects (valve, septum, membrane);
- Cross-sectional area (CSA).
VVs were assessed in the middle part of the neck, in the best visible segment. VVs, similar to the IJVs, were examined in the supine and sitting positions, and the same parameters (except for the presence of intraluminal defects and CSA) were evaluated.

Finally, we evaluated our findings in the context of current sonographic criteria: proposed by Zamboni\(^2\)\(^,\)\(^15\) and the new criteria by expert panel of the International Society for Neurovascular Disease (ISNVD).\(^16\)

Current sonographic criteria (Zamboni’s criteria).\(^17\)

| Q7 | (1) Reflux: constant reflux (>0.8 seconds) in a single IJV or VV, in sitting or supine position; (2) Stenosis/B-mode anomalies: reduction of the CSA of IJV less than 0.3 cm\(^2\) in both body positions, or presence of intraluminal defect (such as webs, septa or malformed valves); (3) No flow: absence of Doppler signal in IJV or VVs in both supine and upright body positions; (4) Negative ΔCSA: CSA of the IJV, which is greater in the sitting position than in the lying position, or appears unchanged despite change in posture; (5) Reflux in intracranial veins (not evaluated in this study): reflux >0.5 seconds in the deep cerebral veins in the sitting and supine position. |

ISNVD sonographic criteria.\(^16\)

| (1) Reflux: bidirectional flow in the IJV in both positions, or bidirectional flow in one position with absence of flow in the other position; (2) Stenosis/B-mode anomalies: reduction of the CSA of IJV less than 0.3 cm\(^2\) in the supine, or presence of an intraluminal defect combined with hemodynamic changes (increased velocity, absence of flow, reverse flow, etc.); (3) No flow: absence of Doppler signal in IJV or VVs in both supine and upright body positions, or in one posture but with bidirectional flow detected in the other position; (4) Negative ΔCSA: CSA of the IJV, which is greater in the sitting position than in the lying position, or appears unchanged despite change in posture. |

**Interpretation of sonographic findings**

We regarded a criterion positive if required parameters were met in at least one segment of the IJV: J1, J2 or J3. We interpreted as reflux (Zamboni’s criterion 1) only completely reversed flow detected in the entire cross-section of the vein. In contrast to some authors, we did not interpret as the reflux a vortical flow, or artefacts produced by whirls in the valve cusps. Since it was very difficult to set a reasonable threshold between ‘normal’ and ‘malformed’ valves (Zamboni’s criterion 2), we interpreted as intraluminal defects all sonographically detectable valves (this rather controversial approach is debated in the Discussion). Also, it was not possible to set such a threshold between ‘normal’ and ‘increased’ flow velocities (ISNVD criterion 2); therefore, we interpreted as the stenosis a presence of intraluminal defects combined with absent or reversed flow.

**Results**

**Catheter venography**

Pathologies were found in 91 out of 116 examined IJVs (78.4%). In 79 cases (86.8%), venous pathology comprised jugular valves compromising the outflow, in 11 cases (12.1%) such abnormal valves in combination with obstructive lesions in the middle and/or upper segments of the IJV and in one case (1.1%) external compression of the middle segment of IJV with normal jugular valve.

Venous outflow abnormalities in at least one IJV were found in 57 patients (98.3%), whereas in one patient (1.7%) no obvious venous pathology was found. Lesions in one IJV were found in 24 patients (41.4%); in 17 patients (29.3%) on the left and in seven patients (12.1%) on the right side. Lesions in both IJVs were revealed in 33 patients (56.9%).

There were also additional venographic findings: stenosis of the left brachiocephalic vein in two patients (3.4%) and significant stenosis of the azygous vein in one patient (1.7%).

**Sonographic examination**

Positive Zamboni’s criteria were demonstrated in 107 of examined IJVs (92.2%): in 75 cases (64.7%) there was one positive criterion, in 21 cases (18.1%) two positive criteria and in 11 cases (9.5%) three positive criteria. Positive ISNVD criteria were revealed in 104 out of 116 examined veins (89.7%). In 54 cases (46.6%), there was one positive criterion, in 27 cases (23.3%) two positive criteria, in 20 cases (7.2%) three positive criteria and in three cases (2.6%) four positive ISNVD criteria. Prevalence of positive sonographic criteria is presented in Table 1. Parameters describing diagnostic
**Table 1** Prevalence of positive sonographic findings in normal and pathological internal jugular veins (IJVs), including separate assessment of the middle part (J2) of the UV

<table>
<thead>
<tr>
<th>Catheter venography</th>
<th>Doppler sonography</th>
<th>CSA, cross-section area; ISNVD, International Society for Neurovascular Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>J2 segment of the vein found abnormal in venography (%)</td>
<td>Positive Zamboni’s criterion: reflux</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Positive Zamboni’s criterion: stenosis/B-mode anomalies</td>
<td>88.0%</td>
</tr>
<tr>
<td></td>
<td>Positive Zamboni’s criterion: no flow</td>
<td>8.0%</td>
</tr>
<tr>
<td></td>
<td>Positive ISNVD criterion: reflux</td>
<td>24.0%</td>
</tr>
<tr>
<td></td>
<td>Positive ISNVD criterion: stenosis/B-mode anomalies</td>
<td>4.0%</td>
</tr>
<tr>
<td></td>
<td>Positive ISNVD criterion: no flow</td>
<td>84.0%</td>
</tr>
<tr>
<td></td>
<td>Positive ISNVD criterion: negative ΔCSA</td>
<td>12.0%</td>
</tr>
<tr>
<td></td>
<td>Positive ISNVD criterion: no flow</td>
<td>24.0%</td>
</tr>
</tbody>
</table>

Catheter venography was used as the reference test.

Diagnostic values of sonographic CCSVI criteria, including likelihood ratios according to the Bayes’ theorem and the Cohen’s kappa coefficient are given in Table 2.

**Table 2** Diagnostic values of sonographic CCSVI criteria, including likelihood ratios according to the Bayes’ theorem and the Cohen’s kappa coefficient

<table>
<thead>
<tr>
<th>Diagnostic value of Zamboni’s and ISNVD sonographic criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive and negative predictive values</th>
<th>Likelihood ratios of a positive and negative result according to the Bayes’ theorem</th>
<th>Kappa (k) coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one positive Zamboni’s criterion</td>
<td>93.4%</td>
<td>12.0%</td>
<td>79.4%/33.3%</td>
<td>93.3%/12.1%</td>
<td>0.136</td>
</tr>
<tr>
<td>At least two positive Zamboni’s criteria</td>
<td>29.3%</td>
<td>75.0%</td>
<td>81.8%/21.7%</td>
<td>94.2%/7.1%</td>
<td>-0.477</td>
</tr>
<tr>
<td>At least one positive ISNVD criterion</td>
<td>90.1%</td>
<td>12.0%</td>
<td>78.8%/25.0%</td>
<td>93.1%/8.4%</td>
<td>0.106</td>
</tr>
<tr>
<td>At least two positive ISNVD criteria</td>
<td>47.3%</td>
<td>72.0%</td>
<td>86.0%/27.3%</td>
<td>95.7%/9.4%</td>
<td>-0.297</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic value of each sonographic criterion</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive and negative predictive values</th>
<th>Likelihood ratios of a positive and negative result according to the Bayes’ theorem</th>
<th>Kappa (k) coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zamboni’s criterion: reflux</td>
<td>89.0%</td>
<td>12.0%</td>
<td>88.0%/23.1%</td>
<td>93.0%/7.7%</td>
<td>0.097</td>
</tr>
<tr>
<td>Zamboni’s criterion: stenosis/B-mode anomalies</td>
<td>20.9%</td>
<td>92.0%</td>
<td>90.5%/24.2%</td>
<td>97.2%/8.1%</td>
<td>-0.563</td>
</tr>
<tr>
<td>Zamboni’s criterion: no flow</td>
<td>23.1%</td>
<td>76.0%</td>
<td>77.8%/21.3%</td>
<td>92.0%/6.8%</td>
<td>-0.563</td>
</tr>
<tr>
<td>ISNVD criterion: reflux</td>
<td>28.6%</td>
<td>96.0%</td>
<td>93.0%/27.0%</td>
<td>98.9%/9.1%</td>
<td>-0.532</td>
</tr>
<tr>
<td>ISNVD criterion: stenosis/B-mode anomalies</td>
<td>82.4%</td>
<td>16.0%</td>
<td>78.1%/20.0%</td>
<td>92.8%/6.4%</td>
<td>0.036</td>
</tr>
<tr>
<td>ISNVD criterion: no flow</td>
<td>33.0%</td>
<td>88.0%</td>
<td>90.9%/26.5%</td>
<td>97.3%/9.1%</td>
<td>-0.439</td>
</tr>
<tr>
<td>ISNVD criterion: negative ΔCSA</td>
<td>23.1%</td>
<td>76.0%</td>
<td>77.8%/21.3%</td>
<td>92.0%/6.8%</td>
<td>-0.563</td>
</tr>
</tbody>
</table>

CSA, cross-section area; ISNVD, International Society for Neurovascular Disease; CCSVI, chronic cerebrospinal venous insufficiency

**Discussion**

Under the conditions of this study, we have found that currently used sonographic criteria for CCSVI are of limited diagnostic accuracy, especially if compared with the results of catheter venography. Actually, some of these criteria were equally represented in the healthy and abnormal veins, while the others could not be demonstrated at all (Table 1). Consequently, statistical coefficients characterizing diagnostic accuracy were unacceptably low (Table 2). These weak points of sonographic assessment of CCSVI will be further discussed.

The use of catheter angiography – a gold standard for the assessment of vascular pathologies – as reference test for the detection of IJV abnormalities could be seen as the strong point of our study. Catheter venography is far more reliable and much less operator-dependent than other diagnostic tests for the assessment of venous flows and anatomy. Still, the use of venography is somewhat weakened by the fact that flow assessment in the IJV territory is a new field of expertise. Probably some valve pathologies were misdiagnosed, since diagnostic catheter inserted in retrograde manner (from the groin) may artificially change morphology of the jugular valve. Besides, we used hand injections of venographic contrast. At the moment, there is no clear consensus on whether during evaluation of the...
IJVs contrast should be hand or pressure injected. Hand injections are performed using smaller volumes of contrast under lower pressure. Pressure injectors are usually higher volume and higher pressure. There are proponents for both approaches. While hand injection mimics physiological venous flow, pressure injectors are more accurate, reproducible and make some flow-related analyses quantifiable. There are some modern injectors that allow low-pressure administration of contrast and perhaps such an equipment should be preferably used. Moreover, for the time being it remains unclear what should be interpreted as normal IJV and what as pathology. While some doctors use an arbitrary definition of 50% luminal restriction of the vein when compared with nominal diameter of this blood vessel, others opt for interpreting such a narrowing as pathological only if accompanied by other flow abnormalities (for example, collateral outflow). Therefore, it cannot be ruled out that our venographic assessment of the IJVs was not always accurate. Probably narrowing of the IJVs should be objectively quantified with the use of intravascular ultrasound (IVUS).

There are also some potential limitations of this study, which are related to sonographic assessment of the IJVs. Examination of the area of junction of jugular vein with brachiocephalic vein (J1) in some patients can be challenging, especially in obese individuals or patients presenting with deep supraclavicular fossa. In the cases of difficult anatomy we used more diagnostic gel and actually in this patient series an adequate visualization of the J1 segment with linear probe was always feasible. An alternative solution is to use small convex probe, which makes appropriate insonation of this area much easier. The other weak point of our study is a lack of sonographic assessment of intracranial veins (one of the Zamboni’s criteria). However, taking into account high rates of false-positive findings of the remaining criteria (Table 1), diagnostic accuracy of the whole set of five Zamboni’s criteria cannot be significantly improved, even if the assessment of intracranial veins were found highly sensitive and specific. In addition, in this patient series we did not find an individual presenting with Zamboni’s criterion 1 (reflux, i.e. a constant backward flow longer than 0.8 seconds). We think that such long-lasting refluxes that are reported in the literature in most of the cases were not real, but actually represented sonographic artefacts resulting from vortical flow. A careful evaluation of doubtful areas exhibiting such ‘refluxes’ (by changing the angle of insonation, widening the Doppler gate, etc.) in almost every case confirmed vortical flow or a twirl within the valve and not a reversed flow. We found reversed flow in IJVs with reflux time >0.8 seconds very infrequently, in less than 1% of CCSVI individuals and not in this patient series (importantly, this caveat applies to the evaluation of IJV at normal breathing, and not during Valsalva, when reflux is a quite common finding). The other questionable point of our study is our interpretation as intraluminal defects all sonographically detectable valves. Taking into account the results of this study presented in Table 1, our approach (i.e. interpreting any visible valve as abnormal) does not look correct. Intravascular defects were equally demonstrated in the veins that appeared normal and abnormal in venography. However, published research and guidelines do not give clear definition of such pathological intraluminal structures. Undoubtedly, this part of sonographic assessment of IJVs needs clarification and perhaps IVUS, instead of standard sonography, should be used to distinguish normal from pathological valves.

At the moment our knowledge about IJV anatomy and physiology is rather scarce. Venographic anatomy of normal jugular vein system has been thoroughly described in the recent review by Werner et al.\textsuperscript{18} Most of the previous studies focused on localization and diameter of these veins, which was of importance during their catheterization in critically ill or dialysed patients. Troianos et al.\textsuperscript{19} examined IJVs in a group of 1136 patients. He did not observe occluded or severely narrowed veins. Denys et al.\textsuperscript{20} found patent and normal-sized right IJVs in 96.4% of 928 critically ill patients (in this particular group infrequently seen occluded IJVs were suspected to be thrombosed after many prior cannulations). Similarly, Lin et al.\textsuperscript{21} found 1.0% prevalence of occluded veins in a group of 104 uremic patients. Other studies focused on jugular valve incompetence.\textsuperscript{22–26} Competent jugular valves are thought to play an important role in establishing physiological venous outflow from the brain in the settings of increased intrathoracic pressure (coughing, Valsalva, blunt chest injury, cardiopulmonary resuscitation, etc.). Incompetent jugular valves may play a role in the pathophysiology of transient global amnesia\textsuperscript{27,28} and transient monocular blindness.\textsuperscript{29,30} There are also a few reports on other structural abnormalities of the IJVs,\textsuperscript{31–33} with uncertain meaning of these anomalies.

In contrast to the above-mentioned pathologies of the IJVs, which are not primarily associated with compromised venous outflow (except for iatrogenic thrombosis), CCSVI patients present with vascular lesions of obstructive characteristics. In most of
the cases these lesions are not related to thrombotic
occlusions. In these patients the most prevalent
abnormality is the stenotic, ‘over-competent’
jugular valve. Using invasive diagnostics (catheter
venography) about 90% of MS patients can be
demonstrated such venous occlusive lesions.13,34–36
Stenotic valves are usually seen in combination
with collapsed middle and/or upper parts of the
IJV. Organic stenoses of the IJVs – not related to
the valve apparatus – are rather infrequently seen.
Thus, majority of CCSVI cases present with valvular
and functional venous abnormalities. Such a unique
vascular pathology is not often seen in the venous
system and no established, non-invasive method
for the assessment of such conditions currently
exists. Unfortunately, all published studies on the
topic of CCSVI were done primarily in the context
of potential association of this vascular pathology
with MS. From the scientific point of view, however,
it seems more accurate to test the validity of one
test (e.g. Doppler sonography) against an established
gold standard test (e.g. catheter angiography) and
not against presence or absence of MS, since the
assumption that there exists a real causation
between MS and CCSVI may be proven wrong. For
the time being, the only published study that has
compared results of Doppler sonography with cathe-
ter venography comes from Zamboni’s group.2 All
65 patients reported in this paper presented with
pathologies revealed by both tests. Unfortunately,
the authors gave no information about lateralization
of Doppler abnormalities and the side of pathologies
demonstrated with venography. In addition to this
pioneer study, several other papers, focusing on
Doppler sonographic assessment of the IJVs in MS
patients, have been published. Still, these studies
did not compare Doppler sonography with reference
test, but rather looked at prevalence of Doppler
abnormalities in MS versus non-MS patients. Inter-
estingly, those studies reported very different fre-
quencies of CCSVI detected in MS patients: from
100% by Zamboni,2,17 through about 90% by
Al-Omari and Rousan37 and Simka et al.,38 50–60%
by Zivadinov et al.39 and Centonze,40 only 10–20%
by Baracchini,41 Murcel42 and Auriel,43 and 0% by
Doeppl,44 Tanaka45 and Tsiovouilis.46 Probably these
very inconsistent results were not a consequence of
differences between the cohorts assessed. Rather,
they resulted from small, but relevant, differences
between protocols and interpretations of the findings.
For example, if the authors have examined only the
middle part of the IJV (J2), where prevalence of posi-
tive criteria for CCSVI is even lower than in healthy
veins (Table 1), most of the lesions would not be
detected. Only Centonze et al.40 and Zivadinov
et al.39 used the same protocol and sonographic
machine as Zamboni, and the sonographers were
trained by his group. But even these authors inter-
preted some of sonographic findings differently,
which undoubtedly resulted in contrasting final
results. There is also a recent report by Monti
et al.,47 where authors using Doppler ultrasound
found non-physiologic cerebral venous outflow
pattern in majority of MS patients (in the supine pos-
tion outflow through vertebral, instead of jugular
veins), contrasting with the normal pattern (outflow
through jugular pathway) in most of the healthy con-
trols.

A high prevalence of venous abnormalities in MS
patients, as has already been demonstrated using
catheter venography,13,34,36,48 makes the search for
a proper non-invasive test rather difficult. Since
venous pathologies are present in majority of MS
patients, theoretically any diagnostic criterion will
reveal high sensitivity and high Bayesian likelihood
ratio. In a case of pathology that reveals high preva-
elence, a reliable test should also be characterized
by high specificity and likelihood ratio of negative
results according to the Bayes’ theorem that is not
much lower than actual prevalence of normal find-
ings (in the case of this study it should not be much
lower than 21.6%). Besides, such a reliable test
should exhibit high Cohen’s kappa coefficient (tra-
ditionally it is interpreted that the kappa higher
than 0.5 indicates a good agreement between the
tests; it should be remembered, however, that in a
case of high prevalence of pathology this threshold
indicating a good agreement is lower than 0.5 and
in the case of this study the value of 0.4 looks reason-
ably).49 Unfortunately, in our study the
kappas of all evaluated criteria were well below
0.4. In several cases these coefficients were even
negative. Thus, their diagnostic values should be
defined as poor or – in the cases of negative
kappa – even worse than that expected to see by
chance alone.

In addition to difficulties in diagnosing CCSVI
properly, understanding clinical significance of
these venous occlusions is not easy.4–6,50 Some
extrapolations could be done from other venous
obstructive syndromes (occlusion of hepatic veins
in Budd–Chiari syndrome or stenosis of iliac vein
in May–Thurner syndrome), but pathophysiology
of the brain and cerebral circulation seems to be
far more complex than those of the liver or the leg.

Our knowledge about prevalence of CCSVI in
non-MS population is even more limited. Of as
yet, a high prevalence of significant obstructions
in the IJV in non-MS individuals was not reported,
but this problem has not been studied thoroughly.
Although Zamboni et al.\textsuperscript{2} has performed venographic assessment of the IJVs and theazygous vein in a small group of non-MS patients and found no venous malformations, his findings should be confirmed by other researches.

It could be summarized that our research has shown that currently used sonographic criteria for the detection of obstructive venous abnormalities in IJVs, the so-called CCSVI, are of limited diagnostic value. Perhaps, a set of reliable criteria for sonographic assessment of CCSVI could be established, but such criteria undoubtedly should differ from those currently proposed. In addition, data on sonographic and angiographic assessment of IJVs in non-MS individuals are too scarce and too inconsistent to draw a sound conclusion. Obviously, more research should be conducted in this field.\textsuperscript{51}

Competing interests

MS received publication fees from Servier International; received speaker fees from American Access Care; received congress costs reimbursement from Esaote International; is employed in the hospital, where the treatments for CCSVI are patient-paid; has applied for research grant on CCSVI sponsored by Polish government (application not yet accepted). TL is employed in the hospital, where the treatments for CCSVI are patient-paid; is the owner of patent on stent design that potentially could be used for the treatment of venous lesions; the stent is not yet available in the market; family member is the owner of hospital where the treatments for CCSVI are patient-paid. PL is employed in the hospital, where the treatments for CCSVI are patient-paid. MK is employed in the hospital, where the treatments for CCSVI are patient-paid.

References


Determinants and clinical significance of jugular venous valve competence. 
Circulation 1982;65:188–96


Tsaladze II. The selective phlebography of the large tributaries of the vena cava system in the diagnosis of venous circulatory disorders in the spinal complex. Zh Vopr Neurokhir Im N N Burdenko 1999;2:8–13


Lane T. Systematic review of sonographic chronic cerebrospinal venous insufficiency findings in multiple sclerosis. Phlebology 2012;20:26
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<td>Q4</td>
<td>Please provide city and state name for Boston Scientific, Cook Medical Inc. and Abbott Vascular.</td>
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<tr>
<td>Q5</td>
<td>Please provide city name for B.Braun and Terumo.</td>
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<tr>
<td>Q6</td>
<td>Please provide manufacturer name and location details for GE LOGIQ-e.</td>
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<tr>
<td>Q7</td>
<td>As font not clear, please confirm the insertion of “delta CSA” here and elsewhere in the text.</td>
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<tr>
<td>Q8</td>
<td>Please provide volume and page range in refs. 3, 18, 40, 42, 43 and 48.</td>
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<tr>
<td>Q9</td>
<td>Please provide the last accessed date for the URL in ref. 9 and 10.</td>
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<tr>
<td>Q10</td>
<td>Please provide the journal name, year of publication, volume and page number in ref. 10.</td>
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<tr>
<td>Q11</td>
<td>Please provide page range in ref. 16 and 36.</td>
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