Internal Jugular Veins Outflow in Patients with Multiple Sclerosis: A Catheter Venography Study

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ABSTRACT

Purpose: To investigate an examiner-independent catheter venography protocol that could be used to reliably diagnose venous outflow abnormalities in patients with multiple sclerosis (MS) and chronic cerebrospinal venous insufficiency and to determine whether venous angioplasty is effective in the treatment of these abnormalities.

Materials and Methods: A total of 313 patients with MS and 12 patients with end-stage renal disease underwent echo-color Doppler sonography and catheter venography of the internal jugular veins (IJVs) to evaluate contrast medium clearance time. In patients with venous outflow anomalies, balloon angioplasty of the IJVs was performed.

Results: A contrast medium clearance time cutoff value of 4 seconds or less provided the maximal combination of sensitivity and specificity for the right IJV (sensitivity, 73.4%; specificity, 100%) and left IJV (sensitivity, 91.4%; specificity, 100%). IJVs with a clearance time between 4.1 and 6 seconds had moderate delayed flow (MDF), and IJVs with a clearance time longer than 6 seconds had severe delayed flow (SDF); 89% of patients showed MDF/SDF through at least one IJV, 79% showed MDF/SDF through both IJVs, and only 5% showed normal flow in both IJVs. Balloon angioplasty was immediately able to improve flow in at least one IJV in 69% of patients, but venous flow was normalized in both veins in only 37% of patients; SDF persisted after angioplasty in 32% of patients.

Conclusions: There is a high prevalence of abnormal delayed flow through IJVs in patients with MS. Venous angioplasty was effective in only a minority of patients with SDF.

ABBREVIATIONS

CCSVI = chronic cerebrospinal venous insufficiency, ESRD = end-stage renal disease, IJV = internal jugular vein, MDF = moderate delayed flow, MS = multiple sclerosis, PP = primary progressive, PTA = percutaneous transluminal angioplasty, ROC = receiver operating characteristic, RR = relapsing–remitting, SDF = severe delayed flow, SP = secondary progressive

Venous phlebography is a well recognized diagnostic technique that is extensively used in the definition of large-vein occlusive disease. Large veins of the thorax and abdomen may be involved in many malignant and benign diseases, and a variety of clinical syndromes are caused by their stenosis or occlusion (1).

Recently, chronic cerebrospinal venous insufficiency (CCSVI) was described as characterized by stenosis in the internal jugular veins (IJVs) and azygos vein, which together provide the venous outflow from the brain and spinal cord (2–9). Various diagnostic modalities have been used to evaluate the controversial problem of quantification of the cerebral venous return, in particular, in patients with chronic neurodegenerative disorders, such as multiple sclerosis (MS) (6–10).

Because of the high variability of venous drainage from the central venous system, it is difficult to use current magnetic resonance (MR) imaging (6,11) to accurately detect the outflow of the IJVs; on the contrary, recent studies (12) have demonstrated that echo-color
Doppler sonography scan techniques are accurate but are also technically challenging and examiner-dependent, and require active collaboration from patients, which leads to highly variable results. Zamboni et al (13) proposed a new cervical plethysmography method that evaluates the cerebral venous return in relation to the change in position, and demonstrated that the cerebral venous return characteristics of patients with CCSVI were markedly different from those of control subjects. Catheter venography demonstrated a high prevalence—always greater than 90%—of venous outflow abnormalities in patients with MS (2,7,14–19). However, despite the use of catheter venography in the diagnosis of CCSVI before treatment, no validated catheter venography scores are now available to classify the anomalous flow patterns of IJVs in these patients. Given this, the purpose of the present study was to evaluate an examiner-independent catheter venography protocol that could be used to reliably diagnose venous outflow abnormalities in patients with MS and to determine if venous angioplasty is effective in the treatment of these abnormalities.

PATIENTS AND METHODS

The study was approved by the ethical committee of the University Hospital of Catania. All patients signed an informed consent form on which the potential risks and benefits of the study treatment were detailed.

This was a prospective, single-center study of a standardized, operator-independent catheter venography protocol to evaluate the hemodynamic patterns in IJVs (as detailed later). The study was unfunded; the Italian National Health System covered all the study’s costs, and the patients and investigators were not paid for their participation.

From May 2011 to September 2012, 313 consecutive patients were referred to our institution with MS. All patients underwent echo-color Doppler sonography of their IJVs in accordance with the recommendations of the international consensus conference on the use of echo-color Doppler sonography in patients with CCSVI (12), followed by catheter venography of their IJVs (Fig 1). An IJV was considered normal if it had no morphologic abnormalities, such as endoluminal defects causing stenosis of the vein (≤ 50% of vein diameter), hypoplasia, or extrinsic muscular compression, and no hemodynamic alterations of venous flow confirmed by sonographic evaluation.

Twelve patients with end-stage renal disease (ESRD; mean age, 48.4 y; eight women and four men) who underwent venography of their IJVs and subclavian veins to evaluate the feasibility of vascular access for hemodialysis were included in the study and considered as control subjects.

The same physician performed all echo-color Doppler sonography evaluations and catheter venography procedures. The patient characteristics and the technical aspects and images from the venography and angioplasty procedures were saved in a database. An independent physician reviewed the images.

The primary endpoints of the study were to define the normal flow time through the IJVs, to detect if a delayed flow time in the IJVs was present in patients with MS, and, in patients with abnormal flow, to determine the immediate efficacy of percutaneous transluminal angioplasty (PTA) in improving the flow.

Patients

A total of 313 consecutive patients with MS were studied for suspected anomalies of venous flow in their IJVs (Table 1).
There was a predominance of female patients (63%). Among the study population, patients with relapsing–remitting (RR) disease were the most predominant cohort (177 patients), followed by those with secondary progressive (SP) disease (95 patients) and those with primary progressive (PP) disease (31 patients). The mean time since MS diagnosis was significantly longer in patients with SP disease (17.8 y vs 8.6 y in RR disease and 11.1 y in PP disease; \( P < .001 \)), whereas the mean age at the time of MS diagnosis was not significantly different among the three groups.

### Catheter Venography of IJVs

All procedures were performed under local anesthesia: because it was necessary for the patient to be conscious and cooperative during the procedure, no further general sedation was used. Access to the venous system was achieved through a percutaneous anterograde approach of the right common femoral vein under sonographic guidance to avoid pain and accidental arterial puncture.

After placement of an 8-F sheath introducer (Boston Scientific, Natick, Massachusetts), an intravenous bolus of 5,000 U of heparin was administered. The right IJV was first cannulated with the use of a 0.035-inch short-angle regular hydrophilic guide wire 260 cm in length (AQUATRACK; Cordis, Bridgewater, New Jersey) supported by a BER II diagnostic catheter (4 F, 100 cm; Cordis). The BER II catheter, a straight catheter with a short distal angulation of the tip, was preferred in view of the goal to minimize possible interference with any endoluminal defects of the IJVs. Before the frame acquisition, for all cases, the BER II catheter was positioned at the level of the jaw angle.

Selective venography of the IJVs was performed by automatic injection of a low-viscosity contrast medium (Iomeron 150; Bracco Imaging, Milano, Italy) in anterior–posterior projection. A low pressure (100 psi) was used to avoid induced reflux. The rate of contrast medium injection was 4 mL/s for 2 seconds (a total of 8 mL for each acquisition). The frame rates were as follows: three frames per second for the first 4 seconds and then two frames per second for 8 seconds, for a total of 28 frames in 12 seconds. The long acquisition time was used to detect a delay of contrast medium clearance through the IJVs. All patients were asked to maintain a straight head and neck position and regular breathing during the frame acquisitions to minimize the venous flow alteration that occurs when a patient holds his/her breath. The same procedure was used for the left IJVs (Fig 2).

Clearance of contrast medium was evaluated before and after percutaneous transluminal angioplasty (PTA) and analyzed prospectively on the basis of catheter venography frames by independent physicians. The contrast medium clearance time was evaluated for analysis in patients with MS and in those with ESRD.

### Venous Angioplasty

IJV angioplasty was performed only in the presence of moderate delayed flow (MDF) or severe delayed flow (SDF) at catheter venography. If endoluminal defects were observed in the presence of a normal clearance time, the vein was not dilated. Compliant balloons of variable diameters (10–18 mm) were chosen to be approximately 10% larger than the native vein diameter. Noncompliant balloons were used only in cases of unsatisfactory results. The balloons were inflated at 8–12 atm to avoid vein damage or rupture for 30 seconds (Fig 3).

The balloon angioplasty was considered effective when it reduced the abnormal delayed flow by at least

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PP (n = 31)</th>
<th>SP (n = 95)</th>
<th>RR (n = 177)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>19/12</td>
<td>36/58</td>
<td>55/122</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>40.9 ± 13.4</td>
<td>44.2 ± 14.8</td>
<td>39.8 ± 13.7</td>
<td>.322</td>
</tr>
<tr>
<td>Mean time from diagnosis (y)</td>
<td>11.1 ± 7.1</td>
<td>17.8 ± 9.1</td>
<td>8.6 ± 6.4</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Right IJV
- \( \leq 4 \) s: 1 11 40
- 4–6 s: 10 31 41
- \( \geq 6 \) s: 20 52 96

Left IJV
- \( \leq 4 \) s: 2 9 18
- 4–6 s: 13 25 48
- \( \geq 6 \) s: 16 60 111

Values presented as means ± standard deviation where applicable.

IJV = internal jugular vein, MS = multiple sclerosis, PP = primary progressive, RR = relapsing–remitting, SP = secondary progressive.
2 seconds. After venous angioplasty, all patients received a fluid load of 1,500 mL overnight to minimize the risk of contrast medium–induced nephropathy.

**Statistical Analysis**

Data are expressed as means ± standard deviation. The Fisher exact test was used for analysis of categoric variables. Differences between means were tested with the two-sided *t* test or the Wilcoxon rank-sum test. A *P* value of less than .05 was used to determine statistical significance.

**RESULTS**

**IJV Clearance Time**

To determine a threshold value for the clearance time of contrast medium that corresponds to normal flow, a receiver operating characteristic (ROC) analysis was performed for catheter venography of the right and left IJVs in patients with MS or ESRD. A clearance time cutoff value of 4 seconds or less provided the maximal combination of sensitivity and specificity for the right IJV (sensitivity, 73.4%; specificity, 100%) and left IJV (sensitivity, 91.4%; specificity, 100%). The complete results of the ROC analysis for catheter venography of jugular veins are displayed in Figure 4. The ROC analysis revealed that left IJVs were more frequently affected by CCSVI than right IJVs (*P* < .001).

The mean contrast medium clearance times in the 12 patients with ESRD and with no signs of IJV stenosis or occlusion was 3.1 seconds ± 0.4, compared with 3.3 seconds ± 0.4 in the 69 IJVs without abnormalities in 57 patients with MS.

Because of the great number of variables that could have influenced flow velocity (systolic pressure, cardiac rate, length and diameter of the IJV, breathing, reduced respiratory capacity in MS, and collateral pathways), to avoid including patients with normal flow occurring between instances of abnormal flow, and based on the results of the ROC analysis, IJVs with a clearance time of 4 seconds or less (ie, frames 7–11) were considered normal.

As a consequence, IJVs with a clearance time of contrast medium between 12 and 15 frames (ie, 4.1–6 s) were considered to have MDF, and IJVs with a clearance time greater than 16 frames (ie, > 6.1 s) were considered to have SDF.

Among the study cohort (313 patients), catheter venography demonstrated a venous outflow abnormality in both IJVs in 73% of patients. For the right IJVs, MDF and SDF were demonstrated in 27.7% and 54.9% of patients, respectively, whereas venous flow was normal
in only 17.2% of patients. For the left IJVs, MDF and SDF were demonstrated in 29% and 61% of patients, respectively, but only 9.9% of patients had normal flow. Normal flow in both IJVs was reported in only 5% of patients (Table 2).

The mean time since MS diagnosis was significantly longer in patients with SP (17.8 y vs 8.6 y in RR and 11.1 y in PPI, P < .001), whereas the mean age at the time of MS diagnosis was not significantly different among the three groups.

There was no correlation between time since MS diagnosis and SDF rate (P = .823), suggesting that MS most likely does not influence the progression of CCSVI (Table 3). Again, there was no correlation between SDF and patient age (P = .854) or between SDF and type of MS (P = .732).

**Angioplasty of IJVs**

Balloon angioplasty was immediately able to improve flow in at least one IJV in 69% of patients, but venous flow was normalized in both IJVs in only 37% of patients; SDF was persistent in 32% of patients (Table 4). The observation of SDF by catheter venography was predictive of poorer results of angioplasty (P < .01).

Among subjects with SDF of the right IJV (188 patients), venous angioplasty determined normal flow in 26.7% and MDF in 29.5% of patients, whereas delayed flow remained unchanged in 43.8% of patients; in left IJVs with SDF (216 patients), after venous angioplasty, 47% of patients had persistent SDF, 29.4% had MDF, and 23.6% had normal flow. Among patients with MDF of the right IJV (68 patients), venous angioplasty established normal flow or MDF in 73% and 27% of patients, respectively; in patients with MDF of the left IJV (62 patients), after venous angioplasty, 66.7% had normal flow and residual MDF was present in 33.3%.

Among the 28 patients with MDF in both IJVs, venous angioplasty normalized flow in both veins in 39.2% of patients; however, venous angioplasty normalized venous flow in only 3.7% of 108 patients with bilateral SDF.

**Figure 3.** Catheter venography of left IJV in a patient with MS. (a) SDF caused by occlusive transversal septa. (b) Excellent morphologic results after angioplasty.
Four patients (1.2%) experienced an inguinal hematoma, which was treated conservatively in each case.

**DISCUSSION**

We have demonstrated, by using a standardized catheter venography protocol, that MS is associated with a quantifiable prolonged clearance time of contrast medium in the IJVs.

CCSVI was first described by Zamboni et al in 2009 (2) as abnormal outflow from the central nervous system to the heart as a result of different anomalies in the main great veins of the neck (ie, IJVs) and chest (ie, azygos vein) (2). CCSVI has been linked to MS, with conflicting results (7,8,20,21).

**Table 2. Hemodynamic Patterns of IJVs in Patients with MS Based on Contrast Medium Clearance Time (N = 313)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Pts.</th>
<th>Normal</th>
<th>MDF</th>
<th>SDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>IJV Right</td>
<td>313</td>
<td>54 (17.2)</td>
<td>87 (27.7)</td>
<td>172 (54.9)</td>
</tr>
<tr>
<td>IJV Left</td>
<td>313</td>
<td>31 (9.9)</td>
<td>91 (29)</td>
<td>313 (61)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 30 y</td>
<td>30</td>
<td>2 (6.6)</td>
<td>12 (40)</td>
<td>16 (53.3)</td>
</tr>
<tr>
<td>31–40 y</td>
<td>83</td>
<td>5 (6.1)</td>
<td>36 (43.3)</td>
<td>42 (50.6)</td>
</tr>
<tr>
<td>41–50 y</td>
<td>127</td>
<td>4 (3.6)</td>
<td>59 (46.4)</td>
<td>64 (50.4)</td>
</tr>
<tr>
<td>&gt; 51 y</td>
<td>73</td>
<td>4 (3.3)</td>
<td>32 (43.8)</td>
<td>37 (50.6)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages.
IJV = internal jugular vein, MDF = moderate delayed flow, MS = multiple sclerosis, SDF = severe delayed flow.

**Table 3. Patients with SDF in IJV Based on Time since MS Diagnosis**

<table>
<thead>
<tr>
<th>Time since Diagnosis</th>
<th>One IJV (%)</th>
<th>Two IJVs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 y</td>
<td>48</td>
<td>36</td>
</tr>
<tr>
<td>5–10 y</td>
<td>56</td>
<td>39</td>
</tr>
<tr>
<td>10–15 y</td>
<td>57</td>
<td>43</td>
</tr>
<tr>
<td>15–20 y</td>
<td>57</td>
<td>37</td>
</tr>
<tr>
<td>&gt; 20 y</td>
<td>55</td>
<td>41</td>
</tr>
</tbody>
</table>

IJV = internal jugular vein, MS = multiple sclerosis, SDF = severe delayed flow.

**Table 4. Immediate Results of PTA of IJV Compared with Preoperative Hemodynamic Flow**

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Flow (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Right IJV Before PTA</td>
<td>Control</td>
</tr>
<tr>
<td>After PTA</td>
<td>40</td>
</tr>
<tr>
<td>Left IJV Before PTA</td>
<td>Control</td>
</tr>
<tr>
<td>After PTA</td>
<td>35</td>
</tr>
</tbody>
</table>

IJV = internal jugular vein, MDF = moderate delayed flow, PTA = percutaneous transluminal angioplasty, SDF = severe delayed flow.

Four patients (1.2%) experienced an inguinal hematoma, which was treated conservatively in each case.

**Figure 4.** ROC curve depicts sensitivity versus specificity of clearance time of contrast medium during catheter venography of right IJV (a) and left IJV (b). (Available in color online at www.jvir.org.)
One of the major concerns regarding the diagnosis of CCSVI and its association with MS is the accurate quantification of cerebral venous return as a result of the inherent variability and complexity of the cerebral venous system. This has generated an increasing interest in the determination of an imaging gold standard for the detection of extracranial venous anomalies.

Echo-color Doppler sonographic evaluation of IJVs requires careful interpretation and is operator-dependent; therefore, to improve the reproducibility of echo-color Doppler sonographic evaluation, a consensus conference defined five criteria for the diagnosis of CCSVI (12). However, this created great variability of prevalence of CCSVI in patients with MS, ranging from 3% to 100% (2,4–8,12,22,23), and the European Society of Neurosonology and Cerebral Hemodynamics expressed considerable concerns regarding the accuracy of these proposed criteria for CCSVI in MS (8).

MR imaging may be useful in the observation of potential CCSVI risk factors (11), but the data regarding this are conflicting, and MR of the venous system has limited value in the assessment of IJV anomalies for diagnostic and post-PTA purposes (5,11,24). Moreover, MR is less sensitive than echo-color Doppler in the definition of intraluminal structural and functional venous abnormalities in patients with MS (12).

Although it is invasive and cannot be used as a screening tool, catheter venography is considered the gold standard for determining the anatomic site, type, and extent of lesions producing CCSVI (2). Membranes, valve malformations, and septa in IJVs are frequently encountered during catheter venography in patients with CCSVI (2–5,10). Catheter venography alone (19,25–28) or in combination with intravascular ultrasound (29) has been used to evaluate the morphological alterations of IJVs in patients with MS.

Currently, the role of catheter venography in the assessment of the hemodynamic patterns of IJVs detected on echo-color Doppler sonography in patients with CCSVI is uncertain (2–4,10), and no validated catheter venography scores are available for the classification of flow patterns of IJVs. Four years since its discovery, the presence of CCSVI as a clinical entity is still controversial: in other words, the challenges at this moment are in defining (i) a definitive diagnostic technique that is able to detect flow abnormalities and variants of IJVs in patients with CCSVI and (ii) the criteria on which to base subsequent treatment decisions.

The present study evaluated a standardized protocol of catheter venography of IJVs in patients with MS by using the clearance time of contrast medium to define the degree of venous flow abnormality. The ROC analysis demonstrated that a venous outflow through the IJVs could be considered normal if the clearance time of the contrast medium was less than 4 seconds. Basing on these findings, the present study found a high prevalence (79%) of venous flow abnormalities of both IJVs, as expressed by a clearance time greater than 4 seconds, in patients with MS, whereas only 5% of patients with MS showed normal venous outflow. The presence of SDF was unrelated to time since diagnosis of MS, suggesting that hemodynamic abnormalities of IJVs are not influenced by the clinical progression of MS.

The increased prevalence of extracranial venous flow anomalies has encouraged the use of angioplasty to treat IJV stenosis with the aim of producing a clinical benefit. Overall, results have not been conclusive (25,30), but, in recent studies, angioplasty was able to reduce the rate of relapse and improve the physical and mental quality of life of patients with MS (10,19,26–28). Angioplasty is a safe procedure (14), but its efficacy in randomized, double-blind trials in patients with MS has not been definitively demonstrated (31). This is partly related to the inability of catheter venography to serve as a gold standard for the detection and monitoring of the extracranial anomalies because there are no hemodynamic parameters that can predict the success of that treatment.

In the present study, angioplasty was able to immediately improve flow in one IJV in 69% of patients, but only in 37% of patients did the venous angioplasty significantly improve the venous flow in both IJVs. Again, in 32% of patients, SDF was persistent after angioplasty, and the presence of SDF was predictive of a worse result after angioplasty.

Most studies have reported early restenosis after balloon angioplasty of IJVs, most likely caused by ineffective treatment, in as many as 45% of cases (19,25–28). Although the results of the present study are promising, we are conscious of its limitations. First, the main challenge of this study was to define what is “normal” by evaluating 12 patients with ESRD and 313 patients with MS without any other venographic alterations. The hemodynamic abnormalities of venous flow in patients with MS were related to the time it took for contrast media to empty from the vein, and this allowed for the stratification of the degree of venous outflow abnormality. Future studies with catheter venography in healthy individuals over a wide range of ages are warranted, although this may be not ethically feasible. Although the present study was not randomized and included a relatively small cohort, it analyzed a homogenous group of patients with similar characteristics, and all the procedures were performed by a single physician with a standardized, non-operator-dependent protocol, which reduced the confounding factors related to the methodology of the procedure. Finally, the endpoint of the study was to evaluate only the immediate efficacy of angioplasty in the treatment of IJV stenosis; therefore, data about the rate of recurrence of IJV delayed flow and data on the clinical course of patients with MS after angioplasty were not included.

In conclusion, by using a non–operator-dependent catheter venography examination, the present study demonstrated a high prevalence of anomalous delayed flow through IJVs in patients with MS. In addition, when SDF was present, the clinical course of MS in those patients did
not interfere with the severity of flow patterns. These data suggest that the anomalous delayed flow of IJs is an independent factor. The present study showed that venous angioplasty is immediately effective in patients with moderate alterations of venous flow, but, in patients with SDF, the efficacy of PTA was clearly evident in only a minority of patients. Ongoing clinical and experimental studies should address the development of new and dedicated devices with the aim of treating all different types of venous anomalies and preventing early recurrences of CCSVI.

REFERENCES