

Extracranial Doppler sonographic criteria of chronic cerebrospinal venous insufficiency in the patients with multiple sclerosis

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Aim. The aim of this open-label study was to assess extracranial Doppler criteria of chronic cerebrospinal venous insufficiency in multiple sclerosis patients.

Methods. Seventy patients were assessed: 49 with relapsing-remitting, 5 with primary progressive and 16 with secondary progressive multiple sclerosis. The patients were aged 15-58 years and they suffered from multiple sclerosis for 0.5-40 years. Sonographic signs of abnormal venous outflow were detected in 64 patients (91.4%).

Results. We found at least two of four extracranial criteria in 63 patients (90.0%), confirming that multiple sclerosis is strongly associated with chronic cerebrospinal venous insufficiency. Additional transcranial investigations may increase the rate of patients found positive in our survey. Reflux in internal jugular and/or vertebral veins was present in 31 cases (42.8%), stenosis of internal jugular veins in 61 cases (87.1%), not detectable flow in internal jugular and/or vertebral veins in 37 cases (52.9%) and negative difference in cross-sectional area of the internal jugular vein assessed in the supine vs. sitting position in 28 cases (40.0%). Flow abnormalities in the vertebral veins were found in 8 patients (11.4%). Pathologic structures (membranaceous or netlike septa, or inverted valves) in the junction of internal jugular vein with brachiocephalic vein were found in 41 patients (58.6%), in 15 patients (21.4%) on one side only and in 26 patients (37.1%) bilaterally.

Conclusion. Multiple sclerosis is highly correlated with chronic cerebrospinal venous insufficiency. These abnormalities in the extracranial veins draining the central nervous system can exist in various combinations. The most common pathology in our patients was the presence of an inverted valve or another pathologic structure (like membranaceous or netlike septum) in the area of junction of the IJV with the brachiocephalic vein.

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Key words: Color Ultrasonography, Doppler, color - Multiple sclerosis - Venous insufficiency.

Multiple sclerosis (MS) is a chronic disease of the central nervous system. This disease was commonly regarded as an autoimmune disorder, although some phenomena associated with MS were difficult to explain on the basis of autoimmunity.¹ The discovery of the so-called chronic cerebrospinal venous insufficiency (CCSVI), which comprises of stenoses and occlusions in the extracranial veins draining the central nervous system: the azygous and the internal jugular veins (IJVs) has shed new light on potential cause of MS.²⁻⁴ It has been recently hypothesized that CCSVI might lead to clinically overt MS, either through activating autoimmune reaction by cerebrovascular endothelium in the settings of refluxing blood flow,⁵ or through noxious activity of iron deposits,⁶⁻⁹ which can be stored in brain parenchyma as a result of breakdown of the blood-brain barrier. It should be emphasized, however, that these hypotheses ought to be proven, both in clinical, as well as experimental settings.

Importantly, significant improvement of clinical symptoms of MS (especially: chronic fatigue, heat intolerance and impaired cognitive functions) after endovascular correction of these venous obstacles^{10,11} favors the idea of direct association of CCSVI with MS. Different venous abnormalities have been found in patients with CCSVI: stenoses, complete occlusions, distortions and intravenously localized pathologic structures (membranes, webs and inverted valves). All these obstacles that profoundly disturb venous outflow

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Figure 1.—Pathologic valve (arrow) in the lower portion of the internal jugular vein.

from the brain and spinal cord are found in very different combinations, regarding the type and the localization.^{3, 4, 12, 13} At the moment, the only published study on a larger group of MS patients, which describes anatomic characteristics of venous lesions comes from Italy.⁴ However, in this study a selected group of MS patients was assessed, with a relatively high percentage of primary progressive cases. This paper presents the findings in a less selected population of MS patients coming from 5 European countries (Poland, Slovakia, Germany, Switzerland and Netherlands).

The aim of this study was to measure in an open-label series the prevalence of extracranial venous flow anomalies according to the criteria elaborated by Italian researches.^{2, 4}

Materials and methods

Seventy patients were assessed (48 women and 22 men) with confirmed diagnosis of MS (according to McDonald criteria).¹⁴ There were 49 patients

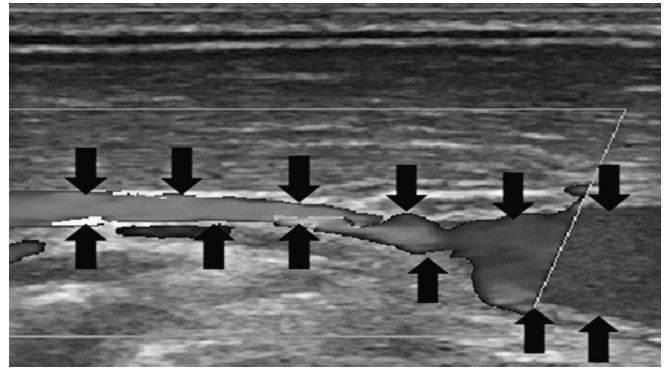


Figure 2.—Significant stenosis of the internal jugular vein (venous contour is marked with arrows).

with relapsing-remitting, 5 with primary progressive and 16 with secondary progressive clinical type of MS (according to Lublin *et al.* criteria¹⁵). The patients were aged 15-58 years; median patients' age was 38.5 years. They suffered from MS for 0.5-40 years; median duration of the disease was 7 years. All examined MS patients were Caucasians and they were citizens of the following European countries: Poland – 45 patients, Slovakia — 14 patients, Germany — 8 patients, Switzerland — 2 patients and Netherlands — 1 patient. This open-label study was the initial step of the ongoing randomized controlled clinical trial on surgical and endovascular treatments for CCSVI. The entire study has been approved by the ethics committee of the local medical university (Silesian Medical University in Katowice, Poland) and the patients have given their consent to have sonographic examination of veins in the neck.

The patients were examined with color Doppler sonography: the IJVs and the vertebral veins (VVs) were assessed. Imaging of the veins was conducted on color Doppler ultrasound machines: GE Logiqe with 7.5-12 MHz linear probe and ATL Apogee 800 with 7.5 MHz linear probe. Examinations were done in the lying and the sitting positions in order to reveal four Zamboni's extracranial criteria of CCSVI: 1) reflux in the internal jugular and/or vertebral veins over 0.88 s; 2) at least 50% stenosis of the proximal internal jugular vein/veins; 3) no detectable flow in the internal jugular and/or vertebral veins; 4) no position-dependent change in diameter of the internal jugular vein/veins.⁴ Because of the lack of special skills and sophisticated software needed on the ultrasonographic system used, we were unable to assess unequivocally

TABLE I.—*Extracranial Doppler sonographic criteria of CCSVI in the present vs. Italian Study.*

Criteria of CCSVI	Present study	Italian study*
Number of patients assessed	70	109
Reflux in IJV and/or VV	31/70 (42.8%)	76/109 (69.7%)
Stenosis in IJV	61/70 (87.1%)	30/109 (27.5%)
Not detectable flow in IJV and/or VV	37/70 (52.9%)	35/109 (32.1%)
Negative Δ CSA* in the IJV	28/70 (40.0%)	61/109 (56.0%)
Reflux in intracranial veins	Not assessed	55/109 (50.5%)
Conclusive analysis: ≥ 2 positive criteria	63/70 (90.0%)	109/109 (100%)
At least one positive parameter	64/70 (91.4%)	109/109 (100%)

*Difference in cross-sectional area of the internal jugular vein assessed in the supine and sitting position.

cally the fifth Zamboni's criterion⁴ (reflux in the deep cerebral veins over 0.5 s), we relied only on the above-described four parameters for assessing the extracranial veins. The IJV, as well as the VVs, have been assessed using a high-frequency linear probe, similarly to the examination of carotid arteries. The probe applied minimal pressure to the skin, in order to prevent undesired compression of the examined vein. The search for venous lesions: stenoses, pathologic valves, etc. (Figures 1, 2) was primarily performed in the supine position, since in this hemodynamic condition the veins were physiologically dilated and therefore it was easier to find pathologies. However, all those veins were also examined in the sitting position, in order to look closer at hemodynamics,¹⁶⁻¹⁸ refluxes that were present only in this body posture and for changes in diameter of the IJVs.^{4, 12}

Statistical analysis

Distributions of venous lesions in the subgroups of the patients (clinical type of MS, sex, duration of the disease and citizenship) were assessed statistically using the χ^2 and the Kolmogorov-Smirnov tests. Significance of these tests was set at $P < 0.05$.

Results

We found at least two of four Zamboni's extracranial criteria in 63 patients (90.0%) and at least one such criterion in 64 cases (91.4%). Thus, we were unable to find an obvious sonographic pathology only in 6 MS patients (8.6%); more than one abnormality was revealed in the examined blood vessels of 64 individuals (91.4%). Compar-

ison of our survey with Italian findings is presented in Table I.

The distribution and characteristics of detected venous abnormalities are summarized in Table II. In our patients no universal anatomical pattern of venous pathology existed. On the contrary, a whole spectrum of stenoses, occlusions and refluxes could be found. The distribution of venous lesions largely varied between patients. Yet, regarding patients' subgroups (clinical type of MS, sex, duration of the disease and citizenship) no statistically significant differences, using the χ^2 and the Kolmogorov-Smirnov tests, have been found.

In general, from the anatomical point of view, three main types of venous abnormalities in the venous system could be demonstrated and in some patients there was a combination of these pathologies.

1. Flow abnormalities in the VVs (refluxing flow, inverted direction of the flow or abnormally low flow rate in the sitting position). Such findings suggested an obstruction in the azygous vein, although, of course, such sonographic signs were only indirect. The stenosis of the azygous vein should be confirmed by means of the standard venography. Such pathologic flow patterns in the vertebral route were found in 8 patients (11.4%). In all these patients, in addition to the signs of compromised outflow through the VVs, there were also obstructions in the IJVs: in 6 patients in one vein and in 2 patients in two IJVs.

2. Pathologic structures (membranous or netlike septa, or inverted valves) were found in the junction of IJV with brachiocephalic vein. Such pathologic structures in some patients were easily demonstrable (Figure 1). In the others this area was poorly accessible, since it was covered by the clavicle.

TABLE II.—Distribution of the sonographic signs of CCSVI in terms of localization of the lesions.

	N. of patients	No pathology revealed in sonographic examination	Sonographic signs of abnormal flow in the azygous vein territory*	Obstacle (e.g. a pathologic valve in the lower part of the IJV)	Obstacle in the lower part of both IJVs	Stenosis of IJV	Stenosis of both IJV	Stenosis of one IJV and obstacle in lower part of the contralateral vein
All patients with clinically defined MS	70	6 (8.6%)	8 (11.4%)	13 (18.6%)	26 (37.1%)	9 (12.9%)	14 (20.0%)	2 (2.9%)
Patients with relapsing-remitting MS	49	5 (10.2%)	3 (6.1%)	8 (16.3%)	16 (32.6%)	8 (16.3%)	10 (20.4%)	2 (4.1%)
Patients with primary progressive MS	5	0	1 (20.0%)	1 (20.0%)	2 (20.0%)	0	2 (40.0%)	0
Patients with secondary progressive MS	16	1 (6.3%)	4 (25.0%)	4 (25.0%)	8 (50.0%)	1 (6.3%)	2 (12.5%)	0
MS patients - men	22	1 (4.5%)	3 (13.6%)	3 (13.6%)	12 (54.5%)	0	6 (27.3%)	0
MS patients - women	48	5 (10.4%)	5 (10.4%)	10 (20.8%)	14 (29.2%)	9 (18.8%)	8 (16.7%)	2 (4.2%)
Patients with history of the disease less than 10 years	44	3 (6.8%)	4 (9.1%)	9 (20.5%)	18 (40.9%)	6 (13.6%)	7 (15.9%)	2 (4.5%)
Patients with history of the disease 10 years and longer	26	3 (11.5%)	4 (15.4%)	5 (19.2%)	8 (30.8%)	3 (11.5%)	7 (26.9%)	0
Patients from Poland	45	4 (8.9%)	6 (13.3%)	7 (15.6%)	13 (28.9%)	6 (13.3%)	14 (31.1%)	1 (2.2%)
Patients from Slovakia	14	0	1 (7.1%)	3 (21.4%)	7 (50.0%)	3 (21.4%)	0	1 (7.1%)
Patients from Germany, Switzerland or Netherlands	11	2 (18.1%)	1 (9.1%)	3 (27.3%)	6 (54.5%)	0	0	0

*All these patients were also found obstructions in the IJVs.

However, indirect signs of such lesions could also be found, for example: dilation of the IJV, low flow rate, or even no detectable flow in this vein, refluxing flow (especially in the lower portion of occluded vein). Such abnormal valves or other pathologic structures in the lower portions of the IJVs were found in 41 MS patients (58.6%). In 13 patients there was an isolated occlusion of one IJV, in 26 patients both IJVs were occluded and in 2 patients there was an obstruction at the junction of the IJV with the brachiocephalic vein coexisting with stenosis of the contralateral vein.

3. Stenoses of the IJVs (Figure 2). These narrowings could be detected either in a short fragment of the vein (usually an increased flow velocity was found in such an area) or, sometimes, such

stenoses extended over a longer distance. In some cases nearly the whole vein was severely narrowed. In the cases with a long stenosis usually a reduced flow rate in this vein was found. Stenoses of the IJVs were present in 25 patients (35.7%), in 9 patients one vein was stenosed, in 14 patients both IJVs were narrowed, while in 2 cases a stenosis on one side coexisted with pathologic valve in the contralateral IJV.

Discussion

Outflow obstructions in the extracranial veins draining the brain and spinal cord are currently defined as chronic cerebrospinal venous insuffi-

ciency.^{3,4} Venous obstacles compromising blood outflow from the brain and spinal cord highly differ between patients, and a whole constellation of venous pathologies can be found, including: occlusions, stenoses, septa and inverted valves. Zamboni *et al.* using standard venography have demonstrated four different patterns of pathologic venous outflows associated with MS: type A characterized by an obstruction of the proximal azygous vein accompanied by a stenosis of one of the IJVs; type B characterized by an obstruction of the proximal azygous vein and bilateral stenoses of the IJVs; type C characterized by bilateral stenoses of the IJVs and the normal azygous vein; and type D characterized by multiple stenoses and occlusions in the azygous vein system.³ These venous pathologies resulted in significant alterations of the flow in the IJVs and VVS, which could be demonstrated by the presence of at least two of five Zamboni's sonographic criteria of CCSVI.⁴

The results of our study are similar to the findings by Italian researches, but some differences should also be underlined. First, we did not find venous abnormalities in all examined MS patients. Since our sonographic systems were unable to assess unequivocally the flow in the intracranial veins and sinuses, we have focused on the examination of the IJVs and the VVs. We thought that from the surgical point of view (the main goal of this study was to screen the patients for potentially operable venous pathologies) such an approach was correct, since in the reports by Zamboni *et al.*³ MS patients exhibited venous occlusions in the extracranial veins, while venous refluxes inside the skull seemed to be secondary phenomena.¹² However, by not performing Doppler scanning of the intracranial vessels, perhaps we were unable to find venous abnormalities in some patients. This may explain why 10% of our MS patients had negative Doppler sonographic test. We suspect, however, that at least some of these patients may have venous abnormalities such as stenoses of the IJVs localized at the level of skull. Such lesions are difficult to find using Doppler sonography. Importantly, some of these patients exhibited sonographic signs, which were suggestive of the presence of a highly-localized lesion, such as an increased flow in VVs in the supine position, but we were unable to confirm such a stenosis with Doppler sonography. Perhaps, MR venography could explain these uncertainties. Of

course, it cannot be ruled out that actually the patients presented with venous flow abnormalities, but we were unable to demonstrate them due to the limited experience in performing such tests.

Second, unlike Italian researches, who have revealed that MS patients presented with at least two venous pathways compromised,³ in this study, but also in our preliminary report,¹³ we demonstrated that some patients with clinically defined MS had occluded only one IJV. In two such cases MR venography (results are not yet published) confirmed that the occlusion was isolated and the contralateral IJV, as well as the azygous vein, were normal. Thus, the distribution of lesions in CCSVI patients is perhaps more complicated and it appears that even occlusion of one IJV (perhaps, in addition to an anomalous intracranial venous anatomy) can result in severe neurological problems.

Moreover, in some patients we found that a stricture in the IJV, visible in ultrasound imaging, was actually a collapse of the vein,^{19,20} probably resulting from a pathologic valve. Importantly, such a problem is difficult to demonstrate with Doppler ultrasound imaging and cannot be diagnosed properly using MR venography. Even intraoperative venography might fail to find the actual lesion, since intravenous catheter can dislocate a pathologic leaflet of the valve, while digital subtraction angiographic imaging from the arterial side might also be insufficient due to the low flow rate in an occluded vein. Therefore, we think that preoperative diagnostics in the patients with CCSVI should primarily consist of Doppler sonography,¹¹ with MR venography serving as an additional test. The results of these two examinations, together with intraoperative venography can give, in our opinion, a whole picture of venous pathology, which seems to be indispensable for the precise endovascular management of such venous abnormalities.

Conclusions

Multiple sclerosis is highly correlated with chronic cerebrospinal venous insufficiency. These abnormalities in the extracranial veins draining the central nervous system can exist in various combinations. The most common pathology in our patients was the presence of an inverted valve

or another pathologic structure (like membranous or netlike septum) in the area of junction of the IJV with the brachiocephalic vein.

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