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Venous Angioplasty in Patients with Multiple Sclerosis: Results of a Pilot Study

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ABSTRACT

Objectives: Chronic cerebrospinal venous insufficiency (CCSVI) is associated with multiple sclerosis (MS). The objective of the study was to see if percutaneous transluminal angioplasty (PTA) of duplex-detected lesions, of the internal jugular and/or azygous veins, was safe, burdened by a significant restenosis rate, and whether there was any evidence that treatment reduced MS disease activity.
Design: This was a case-control study.
Materials: We studied 15 patients with relapsing–remitting MS and duplex-detected CCSVI.
Methods: Eight patients had PTA in addition to medical therapy (immediate treatment group (ITG)), whereas seven had treatment with PTA after 6 months of medical therapy alone (delayed treatment group (DTG)).
Results: No adverse events occurred. At 1 year, there was a restenosis rate of 27%. Overall, PTA was followed by a significant improvement in functional score compared with baseline ($p < 0.02$). The annualised relapse rate was 0.12% in the ITG compared with 0.66% in the DTG (p = NS). Magnetic resonance imaging (MRI) blindly demonstrates a trend for fewer T2 lesions in the ITG ($p = 0.081$), corresponding to a 10% decrease in the ITG compared with a 23% increase in the DTG over the first 6 months of the study.
Conclusions: This study further confirms the safety of PTA treatment in patients with CCSVI associated with MS. The results, despite the significant rate of restenosis, are encouraging and warrant a larger multicentre double-blinded, randomised study.

Chronic cerebrospinal venous insufficiency (CCSVI) is a syndrome characterised by stenosis of the internal jugular and/or azygous veins and formation of collateral venous channels. The stenoses are mainly intraluminal defects, including vestigial membranes, valve malformations and septae.[1–3] Lesions that cause CCSVI have been classified as truncal venous malformations and they are morphological similar to abnormalities known to occur within the iliac veins and inferior vena cava.[4–6]

Extracranial venous obstruction leads to inadequate cerebral drainage. There appears to be a relationship between the severity of extracranial haemodynamic abnormalities and perfusion within the brain parenchyma.[7] The latter can be studied with magnetic resonance imaging (MRI) to assess cerebral blood flow, cerebral blood volume and the mean transit time from the arterial to the venous side of cerebral circulation. In patients with multiple sclerosis (MS), there is evidence that the cerebral blood flow is reduced and the mean transit time increased, suggesting significant abnormalities at the microcirculatory level.[8] There is an association between MRI-detected cerebral flow abnormalities and the Doppler venous hemodynamic insufficiency severity score (VHISS) (Table 1),[7] which has been used to assess the haemodynamic severity of CCSVI.[9,10] The presence of this relationship demonstrates a possible link between extracranial venous outflow obstruction, cerebral microcirculatory changes and the course of patients' MS.[7–10]

Duplex scanning uses a combination of physiological measurements as well as anatomical imaging, and is the proper tool for screening, permitting flow evaluation in different postural and respiratory conditions.[1–3] Duplex has been tried by different centres with variable results.[1,11–15] A high prevalence, ranging from 62% to 100% of obstructive lesions, has been found by some teams in patients with MS compared with low prevalence (0–22%) in controls.[1,11–13] However, absence of such lesions or a lower prevalence has been reported by others.[14,15] This variability could be the result of differences in technique, training, learning curve or criteria used.[16]

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Table 1
Abbreviations used in the article.

9HPT	9-hole peg test
AT	Acquisition time
AZ	Azygous vein
CAL	Combined active lesions
CCSVI	Chronic cerebrospinal venous insufficiency
C.O.N.S.O.R.T.	Consolidated Standards of Reporting Trials
CVIMS	Chronic venous insufficiency in MS
DEVT	Delayed endovascular treatment group (operated 6 months from baseline)
DMT	Disease-modifying therapy
DS	Doppler sonography
DTPA	Diethylene triamine pentaacetic acid
ECD	EchoColor-Doppler
ETL	Echo train length
EDSS	Expanded disability status scale
EVT	Endovascular treatment
EVT-MS	Endovascular treatment study for MS
FA	Flip angle
FLAIR	Fluid attenuated inversion recovery
FOV	Field of view
FSE	Fast spin echo
FSPGR	Fast spoiled gradient echo
Gd	Gadolinium
HC	Healthy controls
HDNV	Multi-channel head and neck coil
HIRES	3D high-resolution
IEVT	Immediate endovascular treatment group of patients (operated at baseline)
IJV	Internal Jugular Vein
IR	Inversion recovery
IRB	Institutional review board
LV	Lesion volume at MRI, assessed both in T1 and T2
LVV	Lateral ventricle volume
MS	Multiple sclerosis
MRI	Magnetic resonance imaging
MSFC	Multiple sclerosis functional composite
NABT	Normal-appearing brain tissue
PASAT	Paced auditory serial addition test
PBVC	Percent brain volume change
PD	Proton density
PTA	Percutaneous transluminal angioplasty
RR	Relapsing–remitting
SE	Spin echo
SIENA	Structural image evaluation using normalization of atrophy
SIENAX	Structural image evaluation using normalization of atrophy, cross-sectional
SPSS	Statistical package for the social sciences
T25FW	Timed 25-ft walk
TE	Echo time
TI	Inversion time
TR	Repetition time
VH	Venous haemodynamic
VHISS	Venous haemodynamic insufficiency severity score
WI	Weighted image

In a group of patients affected by MS, percutaneous angioplasty (PTA) of CCSVI was reported to be feasible as a day surgery treatment, with a minimal complication rate.[2] Postoperative venous pressures were significantly reduced. This method was criticised because of the lack of a control group and blinded, objective MRI measurement. The study was also criticised for using a potentially dangerous treatment without evidence of neurological and vascular safety.[17]

The present study was designed to address these criticisms and to determine whether treatment of CCSVI with PTA affected disease progression in patients with MS.

Methods

Participants

Sixteen patients with MS, who had been the subjects in the chronic venous insufficiency in MS study (CVIMS),[7,9,10,18] were asked to participate. The CVIMS was a pilot collaborative study between the University of Buffalo and the Universities of Ferrara and Bologna, Italy that involved patients with relapsing–remitting MS[19] and age- and sex-matched healthy controls. All the patients with MS fulfilled the duplex ultrasound CCSVI venous haemodynamic (VH) criteria. The duplex prevalence of CCSVI in MS was 100%, whereas, in eight normal subjects used as controls in the CVIMS studies, the prevalence was 0%.[7,9] Of the 16 patients, 15 met the inclusion/exclusion criteria and agreed to participate (eight from Italy and seven from Buffalo).

Inclusion criteria were: patients with a diagnosis of MS according to the McDonald criteria,[19] who were on treatment with Food and Drug Administration (FDA) – approved disease – modifying treatments and who were aged between 18 and 65 years. Their expanded disability status scale (EDSS) had to range from 0 to 5.5, they had to have more than two areas of abnormal extracranial cerebral venous outflow that met VH criteria[1,2] and had to have normal kidney functioning (creatinine clearance >59 ml/min).

Exclusion criteria were: pregnancy, relapse of MS, disease progression and steroid treatment within the 30 days preceding study entry, pre-existing medical conditions known to be associated with brain pathology (e.g., neurodegenerative disorder, cerebrovascular disease, positive history of alcohol abuse and so on) and contraindication for receiving gadolinium (Gd)-based contrast agents.

Design

The study was designed to have half of the cohort treated at baseline (immediate treatment group (immediate), four from Buffalo and four from Italy) and half of the cohort delayed for 6 months (delayed treatment group (delayed)). Patients were selected randomly to undergo PTA immediately after baseline screening. For the Buffalo MS patients, group selection was simply based on the availability of an international travel document (only four patients had passports available at baseline, whereas the three patients assigned to the delayed group needed to wait to obtain one). The Italian patients were randomly assigned to their groups by alphabetical order. Fig. 1 illustrates the study design, in accordance to CONSORT (Consolidated Standards of Reporting Trials) requirements.

All interventions took place in Ferrara, Italy. Catheter venography of the major extracranial and extravertebral segments of the cerebrospinal veins was done according to a protocol previously described.[2] Patients were then given 5000 IU of intravenous heparin and the lesions identified were treated with PTA. Lesions of the azygous vein were treated with 8–10-mm-diameter angioplasty

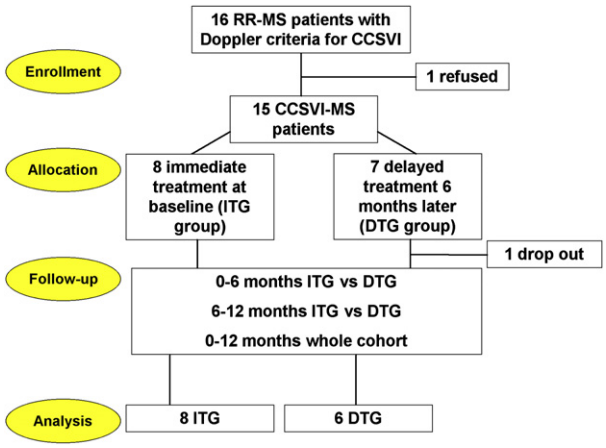

Figure 1. Flow diagram of the EVT-MS study.

balloons between 2 and 6 cm in length, inflated to a maximum pressure of 8 atm. Inflations were held for 30–60 s and repeated several times, as required.

PTA of stenosed internal jugular veins was performed first with a compliant balloon (10–12 mm diameter, 2–4 cm length), which was then inflated to 8 atm. Smaller-calibre balloons were selected in cases of severe atresia or segmental hypoplasia. The compliant balloons were used not only for therapeutic dilation but also as a means of assessing the resistance of the stenosis and the degree of wasting of the balloon during maximum dilation. In the event of a poor post-procedural outcome, the treatment was repeated with a non-flexible high-pressure balloon (18–20 atm) of equal diameter and length to the compliant balloon.

End points

The primary end points of the study were safety, patency rate and the effect of PTA on brain lesions, as well as relapse rate. These were investigated by monitoring adverse events related to PTA at 1, 6 and 12 months. The effect of treatment was measured by the annualised relapse rate and the proportion of patients who were relapse-free in each group. Brain lesions were assessed by counting the number of new active lesions on T2- and T1-weighted post-contrast MRI serial scans and changes in lesion volumes (LVs). MRI assessment was done at baseline, 6 and 12 months.

The secondary end points of the study were to investigate the efficacy of immediate vs. delayed PTA on clinical outcomes (relapse rate, EDSS, multiple sclerosis functional composite (MSFC)) and changes in whole brain volume (percent brain volume change (PBVC)).

Clinical outcome measures

All patients underwent neurological examinations, EDSS scoring and MSFC evaluations followed by duplex ultrasound at baseline, 3, 6, 9 and 12 months. In addition, the rate of annualised relapse rate and the percentage of patients relapse-free were assessed. EDSS was done by neurologists specialising in MS, whereas the MSFC was performed by a credentialled researcher.

Neurological outcome measures usually adopted in clinical trials in MS were used including, the authors' first open-label evaluation of PTA.[2] The Kurtzke EDSS is a method of quantifying disability in MS. The EDSS categorises a person's level of disability.[20] EDSS scores range from 0 to 10, with higher scores indicating more severe disability. It is an important tool in clinical practice because it is widely used and takes a snapshot of the clinical situation.

The MSFC is a multidimensional clinical outcome measure consisting of quantitative timed tests of leg function/walking (Timed 25-Foot Walk, T25FW), group function (Nine-Hole Peg Test, 9HPT) and cognitive function (paced auditory serial addition test, PASAT) expressed as a single score along a continuous scale.[21,22] The composite score was calculated by adding the *z*-scores obtained and dividing the sum by 3, as described in the following formula: MSFC Score = (*z*-arm, average − *z*-leg, average + *z*-cognitive, average)/3.0. *Z*-score is a method of standardisation, a process that leads a random variable distributed according to an average μ and variance σ^2, a random variable with distribution of 'standard', that is, 0 mean and variance of 1.

MRI assessments and analysis

Image acquisition

MR assessments were done at the University of Buffalo, USA. All subjects were examined in a 3T GE Signa Excite HD 12.0 Twin Speed 8-channel scanner (General Electric, Milwaukee, WI, USA), with a maximum slew rate of 150 T m^{-1} s^{-1} and maximum gradient amplitude in each orthogonal plane of 50 mT m^{-1} (zoom mode). A multi-channel head and neck (HDNV) coil manufactured by GE was used to acquire the following sequences: two-dimensional (2D) multiplanar dual fast spin echo (FSE) proton density (PD) and T2-weighted image (WI); fluid-attenuated inversion recovery (FLAIR); and three-dimensional (3D) high-resolution (HIRES) T1-WI using a fast spoiled gradient echo (FSPGR) with magnetisation-prepared inversion recovery (IR) pulse and spin echo (SE) T1-WI with and without using a single-dose intravenous bolus of 0.1 mMol kg^{-1} Gd-diethylene triamine pentaacetic acid (Gd-DTPA) 5 min after injection. All scans were prescribed in an axial–oblique orientation, parallel to the subcallosal line.

Lesion measures

The lesion-activity analysis was performed between baseline and 6 months and 6 and 12 months by identifying the number of new active lesions and active scans. A new Gd-enhancing lesion was defined as a typical area of hyperintense signal on post-contrast T1-weighted image. Other Gd-based MRI lesion-activity outcomes included the number of total Gd-enhancing lesions per patient and the number of persistent Gd-enhancing lesions (enhancing lesions were also present on the previous scan). A new or newly enlarging lesion on T2-weighted images was defined as a rounded or oval lesion arising from an area previously considered normal-appearing brain tissue (NABT) and/or showing an identifiable increase in size from a previously stable-appearing lesion. Other T2-based MRI lesion-activity outcomes included the number of newly enlarging, persistently enlarging or recurrent T2 lesions. The authors also determined the number of combined active lesions (CALs), defined as new enhancing lesions plus the number of new or newly enlarging, non-enhancing lesions on T2-weighted image. The T2- and T1-LVs (T1-LV andT2-LV) were measured using a semi-automated edge-detection contouring/thresholding technique previously described.

Global and central brain volume measures

For brain extraction and normalized brain volume (NBV) estimation, the structural image evaluation, using normalization, of atrophy cross-sectional (SIENAX) software tool was used, with in-house-developed corrections for T1-hypointensity lesion misclassification. PBVC was measured using the structural image evaluation, using normalization, of atrophy (SIENA) method. The baseline scan was co-registered with the follow-up scan at any time point, and an analysis of relative edge motions was used to calculate the PBVC between all available time intervals. The lateral ventricle volume (LVV) was calculated using a semi-automated approach.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, Version 16.0) by an independent statistician. For comparisons between the groups, the two-tailed Fisher exact test, the Student's *t*-test, the Mann–Whitney *U* test and the Wilcoxon rank sum test were used, as appropriate. The minimum significance was 0.05. All *p* values were based on two-tailed tests.

Results

Baseline characteristics

There were no significant baseline demographic differences between MS patients (Table 2). All patients were on disease-modifying therapy (DMT, Table 2) unchanged for at least 6 months before enrolment. Table 2 also displays the venous duplex

Table 2
Baseline characteristics in multiple sclerosis patients (total and according to the treatment group).

	Multiple sclerosis ($n = 15$)	Immediate Treatment Arm ($n = 8$)	Delayed Treatment Arm ($n = 7$)
Female gender, N (%)	10 (66.7%)	4 (50.0%)	6 (85.7%)
Age y.o., median (range)	36 (23–49)	36 (23–49)	36 (31–38)
Age at Onset y.o., median (range)	28 (15–44)	29.5 (15–44)	27 (23–30)
Disease Duration y., median (range)	8 (5–10)	7 (5–9)	8 (5–10)
Number of Relapses in the year prior to baseline, median (range)	0 (0–2)	0 (0–2)	0 (0–1)
Number of Relapses in the year prior to baseline, N (%)			
0	12 (80.0)	7 (87.5)	5 (71.4)
1	2 (13.3)	–	2 (28.6)
2	1 (6.7)	1 (12.5)	–
EDSS, median (range)	2.5 (1.5–5.5)	2.0 (1.5–5.5)	3.0 (1.0–3.5)
MS Functional Composite Components (mean, SD)			
PASAT (Number Correct)	45.5 (9.5)	46.3 (12.6)	44.6 (5.2)
25 foot timed walk (sec)	4.9 (1.1)	5.0 (1.3)	4.7 (0.9)
9 hole peg test dominant hand (sec)	23.5 (7.2)	22.8 (2.8)	24.4 (10.5)
Disease-modifying therapy in the year prior to baseline, N (%)			
Interferon-beta 1a	10 (66.7%)	5 (62.5%)	5 (71.4%)
Glatiramer acetate	2 (13.3%)	1 (12.5%)	1 (14.3%)
Natalizumab	3 (20.0%)	2 (75.0%)	1 (14.3%)
Number of VH Criteria fulfilled, median (range)	4 (2–5)	4 (2–5)	4 (3-5)
VH Criteria Met, N (%)			
1	11 (73.3)	6 (75.0)	5 (71.4)
2	14 (93.3)	7 (87.5)	7 (100.0)
3	13 (86.7)	7 (87.5)	6 (85.7)
4	13 (86.7)	7 (87.5)	6 (85.7)
5	7 (46.7)	4 (50.0)	3 (42.9)
Total number of GAD enhancing lesions, median (range)	0 (0–5)	0 (1-5)	0.0 (0.0)
Total volume of GAD enhancing lesions, cm^3, median (range)	0 (0–0.16)	0 (0–0.16)	0.0 (0.0)
T2 Lesion Volume, cm^3, median (range)	4.9 (1.5–37.8)	4.1 (1.5–37.8)	4.9 (3.2–9.9)
T1 Hypointense Lesion Volume, cm^3, median (range)	1.2 (0.08–11.9)	1.2 (0.08–11.9)	1.2 (0.4–5.7)
Normalized BV, cm^3, median (range)	1528.6 (1280–1612.8)	1588.1 (1490.4–1621.4)	1478.6 (1280–1612.8)
Lateral Ventricle Volume, cm^3, median (range)	15.6 (3–39.7)	14.6 (3–32.1)	20.6 (6.7–39.7)

Legend: N – number; EDSS – Expanded Disability Status Scale; VH – venous haemodynamic; GAD – gadolinium; BV – brain volume. All volumes are expressed in centimeter cubes (cm^3).
The data for delayed treatment group are shown at baseline. Delayed treatment arm started the endovascular treatment after 6 months of follow-up and the patients were followed for another 6 months.

ultrasound haemodynamics criteria and MRI characteristics in the patients.

Safety and tolerability

Venography confirmed duplex diagnosis of CCSVI in 100% of cases. No adverse events or major complications were reported, including bleeding, allergy and problems related to contrast media. Patients were discharged the same day. One case of vasovagal syncope was reported 3 h after the procedure. One dropout occurred in the delayed group at the 3 months' follow-up for familial reason.

Restenosis

Overall, restenosis occurred at 1 year in 27% of cases. Restenosis was detected by means of duplex ultrasound in four patients, in two in the delayed group at 9 months follow-up and one in the delayed and one in the immediate group at 12-month follow-up. Restenoses were confined to the jugular veins.

Clinical outcome measures

There were five relapses during the study, one in the immediate group and four in the delayed group. The annualised relapse rate was 0.12% in the immediate group compared with 0.66% in the delayed group. Seven out of eight patients (88%) were relapse-free at 1 year in the immediate group compared with three of six (50%) in the delayed group (p = NS). The one relapse in the immediate group occurred in a patient who presented at 12 months with 16 new CALs. In the delayed group, one patient had two relapses and two patients had one relapse.

There were no significant changes in EDSS over 12 months between the two treatment groups. There was significant improvement in MSFC compared with baseline over 0–6 months ($p < 0.02$) and 0–12 months ($p < 0.02$) in both immediate and delayed groups.

MRI outcome measures

Details of primary and secondary MRI end points are given in Table 3, as well as T2-, T1- and Gd-LV changes over the follow-up period. There was a trend for lower accumulation of T2-LV in the immediate group over 0–6 months (−5.8% vs. +23%, $p = 0.081$). Further, the decrease of T1-LV was higher in the immediate group compared with the delayed group over 12 months (−36.8% vs. −13.5%, p = NS).

At 6 months, brain volume was reduced by 1.35% in the immediate group, compared with 0.8% in the delayed group. At 12 months, the figures were 0.82% volume reduction in the immediate group and 0.82% in the delayed group. No differences in lateral ventricular volume were seen between the groups after 12 months.

The mean number of new CALs was 4.5 in the immediate and two in the delayed group. The increased number of new active lesions in the immediate group was mainly because of the increased activity detected in just one MS patient, who presented with 16 new CALs and the relapse.

Table 3
Primary and secondary MRI endpoints in multiple sclerosis patients (according to treatment group).

	IEVT Group at 6 months ($N = 8$)	DEVT Group at 6 months ($N = 6$)	IEVT Group at 12 months ($N = 8$)	DEVT Group at 12 months ($N = 6$)
Total number of new CAL, median (range) sum	0.5 (0–3) 12	1.5 (0–3) 5	3 (0-16) 36	1.5 (0-6) 12
Active CAL scans in individual patients, N (%)	6 (75)	3 (50)	5 (62.5)	4 (66.7)
Total number of new Gd lesions, median (range) sum	0	0	0 (0–9) 9	0 (0-1) 1
Active Gd scans in individual patients, N (%)	0	0	1 (12.5)	1 (16.7)
Total number of new T2 lesions, median (range) sum	0.5 (0–3) 12	1.5 (0–3) 5	3.5 (0–13) 34	1.5 (0–5) 12
Active T2 scans in individual patients, N (%)	6 (75)	3 (50)	4 (50)	4 (66.7)
T2-LV % change, median (range)	−8.9 (−52.5 to +15.6)	+19.4 (−10.3to+74)	−3.8 (−55.6to+32.8)	+20.3 (−26.3 to +78.5)
T1-LV %, median (range)	−37.6 (−36.3 to +52.7)	−31.2 (−72.4 to +3.8)	−36.8 (30.1)	−15.2 (−53.4 to +28.4)
PBVC, median (range)	−1.27 (−6.6 to +1.1)	−0.57 (−1.8 to −0.3)	−0.69 (−3.3 to +0.9)	−0.84 (−1.1 to +1.4)
LVV % change, median (range)	+1.2 (−17 to +7.2)	+5.6 (+0.0 to +14.2)	+9.2 (−6.2 to 16.4)	+2.3 (−9.7 to +10.9)

Legend: CAL – combined active lesion; Gd – gadolinium; LV – lesion volume; PBVC – percent brain volume change; LVV – lateral ventricle volume.
PBVC was obtained using automated SIENA technique. LVs and active lesions were assessed by a semi-automated method. LVV was calculated by manual measurement.

Discussion

Safety of endovascular treatment of CCSVI has been evaluated in a large observational study in 564 consecutive cases; major complications including rupture, thrombosis and stent migration were not reported at all, whereas minor complications were observed in 2% of cases.[23] Our study confirms that PTA in expert hands is safe and well tolerated.[2] PTA is a conservative treatment and does not expose patients to the risks of migration or other complications related to the use of stents.[2,4,17]

In the present study, measurement of MRI lesion activity was especially used for further safety purposes because, prior to this study, little was known about the neurological consequences of venous PTA in the brain. Lesion activity was increased in the immediate group with respect to the delayed group; however, this effect was mostly driven by high activity in one patient, who accounted for 16 new CALs. The two hypotheses for explaining this paradoxical effect are that (1) the patient did not respond to PTA or (2) reopening of the veins increased perfusion of the microcirculation of the brain parenchyma, which resulted in short-term inflammation. There may be other reasons. This specific patient had a very active disease.

In the present study, the restenosis rate was lower than previously reported, being 27% compared with 47%.[2] Interestingly, restenosis was observed exclusively in the territory of the jugular vein and not at all in the azygous vein. This finding confirms that PTA may be an appropriate treatment for the azygous vein, with a high probability of success at the first attempt (Fig. 2).[2]

PTA was followed by a significant improvement in MSFC ($p < 0.02$).[2] MSFC was chosen as outcome measure because it is considered a detailed test assessing the disability in MS; it integrates motor function of the lower and upper extremities, coordination and cognitive function, and is highly recommended in MS clinical trials.[21,22]

MSFC changes usually require longer than a 1-year follow-up period to provide a significant clinical change in large MS trials. From this point of view, this finding is particularly interesting in our study. The authors did not prevent the possible improving effect related to the practice of the MFSC test by the patients because they also used the additional control measure EDSS that does not include this effect. The EDSS stability confirms the significant improvement of MFSC.

In a previous study, there was also reported a significant reduction of the number of relapse-free patients following venous angioplasty.[2] By comparing the groups over 0–6 months, the annualised relapse rate and the percentage of relapse-free patients were, respectively, 0.12% and 88% in the immediate group and 0.66% and 50% in the delayed one. The decreased relapse rate

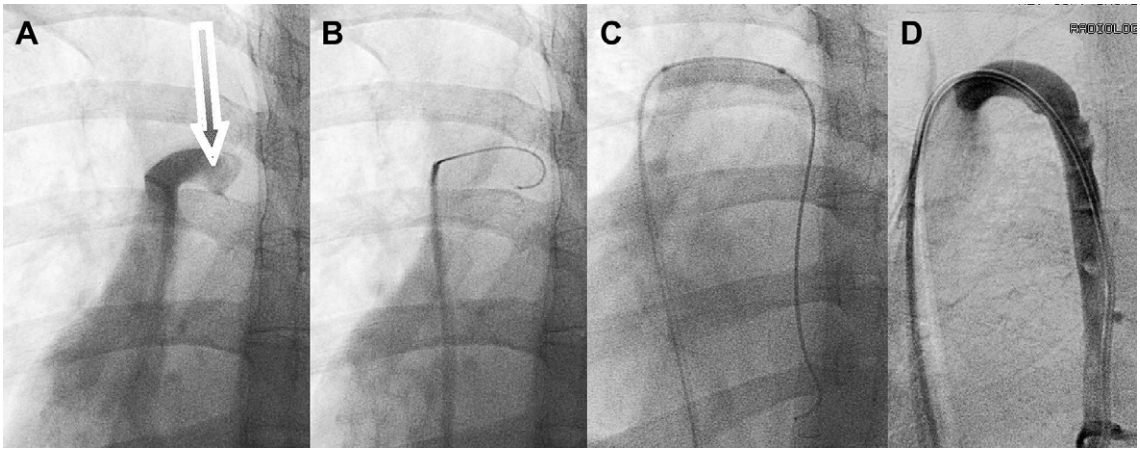

Figure 2. A) Catheter venography depicts a membranous obstruction at the level of the azygous arch (arrow). It has been described in some cases as a possibility for a rudimental valve apparatus. However, this is located at the outlet with the superior vena cava and is confined to the venous wall without significant protrusion in the lumen. B) The guide wire is rejected by a membranous obstruction. C) After perforation of the membrane the balloon is inflated. D) Postoperative control demonstrates the patency of the azygous vein.

demonstrated in the immediate group compared with the delayed group, albeit not significant, seems to indicate that PTA could potentially enhance the effect of medication given to patients with MS.

There was a trend for lower accumulation of T2 LV on MRI in the immediate group ($p = 0.081$), corresponding to a 10% decrease in the immediate group compared with a 23% increase in the delayed group over the first 6 months. This difference was maintained over the 12-month follow-up. The potential therapeutic role of PTA is apparently confirmed by the higher decrease in the T1-LV in the immediate group compared with the delayed group over 0–6 months.

One problem with every potential anti-inflammatory therapy used in patients with MS is that each of them decreases whole brain volume more rapidly in the treated vs. the placebo group due to reduced inflammation in the first couple of months of treatment, with any beneficial effect only becoming evident afterwards. This accelerated-treatment-related brain-volume reduction is known as 'pseudoatrophy'.[24] The higher percent brain-volume change decrease over the first 6 months (−1.35%) in the immediate group suggests a more pronounced pseudoatrophy effect compared with the delayed group (−0.8%), possibly because of a potential anti-inflammatory effect of PTA. Alternatively, a decrease in brain volume might be because of better venous drainage following angioplasty.[25,26] No differences were seen over 12 months between the two treatments groups.

The aetiology and pathogenesis of MS remain largely unknown. It is believed to be an immune-mediated disorder of multifactorial origin.[27,28] MS association with CCSVI have been found in duplex ultrasound studies.[1,11–17] This cohort of patients was a part of the CVIMS studies presenting a 100% prevalence of CCSVI in MS vs. 0% in controls.[7,9] In the present study, this prevalence was further validated by venography.

In addition, CCSVI shares common genetic components with MS,[29] may cause significant transstenotic gradient of venous pressure[2] and, finally, is associated with abnormal cerebrospinal fluid dynamics[9,10] as well as with hypoperfusion of brain parenchyma.[7] The above findings support a role of CCSVI in MS pathogenesis.

Moreover, from a clinical point of view, the reduction of chronic fatigue after venous PTA in MS patients seems to indicate this as a peculiar symptom of CCSVI in the complex MS picture.[30] The accepted possibility of a multifactorial pathogenesis has, of course, therapeutic implications because more than one approach to treatment may be required in curing this disease effectively.[27] From this point of view, PTA could be a further therapeutic contributor to the management of MS.[2]

PTA of venous lesions cannot be recommended as a treatment for MS based on the results of this study. However, our data confirm that treatment of CCSVI was related to changes in the clinical and MRI outcome measures of patients with MS, and warrant a trial with large number of patients and double-blind methodology to minimise the placebo effect.

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Conflict of Interest

Paolo Zamboni received a grant from Hilarescere Foundation, and technical equipment from Esaote Biomedica.

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