FIXING THE JUGULAR FLOW REDUCES VENTRICLES VOLUME AND IMPROVES BRAIN PERFUSION.

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ABSTRACT

Objective: Increased ventricles volume and brain hypoperfusion are both linked to neurodegeneration. We hypothesised that patients with restricted jugular flow may reduce brain ventricles volume by surgical restoration, which in turn ameliorate the pressure gradient so favouring fluid re-absorption into the venous system. We also verified the effects of the procedure on cerebral perfusion.

Methods: 56 patients (M28/F28 mean age 44±10) with Eco-Colour Doppler (ECD) screening positive for chronic cerebrospinal venous insufficiency (CCSVI) in consequence of not mobile jugular leaflets, were further studied by the means of a validated ECD protocol of flow quantification, MRV and SPECT-CT. Fifteen patients were excluded because did not meet inclusion and exclusion criteria. Of the remaining 41 patients, 27 patients (M14/F13 mean age 48 ±7) underwent to endophlebectomy and autologous vein patch angioplasty. Omohyoid muscle section was performed when appropriate. The control group was constituted by 14 patients matched for age and gender (M8/F6 mean age 43±11), who were not treated. Comorbidity was multiple sclerosis with not significant differences of relapsing remitting (RR) and secondary progressive (SP) clinical course among groups. Main outcome measure was the cerebral ventricles volume, blindly assessed at SPECT-CT. Secondary outcomes were brain perfusion in the whole brain and in other 12 cerebral regions, and 18 months jugular patency.

Results: in the cohort of 41 cases, jugular and collateral flow, ventricles volume and brain perfusion were significantly different from normal reference values. Moreover, in the control group, both ECD and SPECT-CT did not show any significant changes at follow-up. To the contrary, in the operated group, the collateral flow passed from 65% to 26% ($p<0.0003$), thanks

to improved flow through the internal jugular vein. Correspondingly, ventricles volume dramatically decreased in the treated group (from 33.5 ± 13.6 cm^3 to 31.3± 13.1 cm^3; p< 0.0106). The effect was much more evident in RR (p=0.0098) whereas in SP was not significant. Finally, perfusion was found improved in the surgical group respect to controls, particularly in the occipital and parietal regions of RR (p<0.0001; p=0.0168; respectively), but in the SP subgroup did not. Eighteen months patency rate was 73%.

Conclusion: fixing the flow in the jugulars in patients with CCSVI might significantly reduce brain ventricles volume and improve cerebral perfusion, and these changes are more evident in patients with earlier stages of neurodegenerative disease.

INTRODUCTION

Chronic cerebrospinal venous insufficiency (CCSVI) is a condition characterized by restricted venous outflow from the brain, mainly in consequence of not mobile/defective valve leaflets[1-6] eventually coupled with muscular compression,[7-8] striking the internal jugular (IJV) and/or azygous veins. The more frequent cause are defective valves and intraluminal obstacles, which can be documented with a combination of techniques (intra and extravascular ultrasounds, catheter and MR venography). CCSVI intraluminal obstacles are classified among truncular venous malformations.[1,9]

Particularly, the venous flow through the IJV was assessed significantly slow, by the means of different invasive and non-invasive techniques, whereas the blood volume flowing into the collateral vessels was measured increased respect to healthy controls.[10-14]

One of the main questions is the patho-physiological consequence in the brain of extracranial venous pathology. Investigations along years in this field identified a significant impact of

CCSVI on two main aspects, respectively cerebrospinal fluid (CSF) dynamics and brain perfusion.

i) Several studies in case of jugular flow disturbances measured altered CSF dynamics, in consequence of reduced absorption of the fluid into the dural veins, in turn connected with the IJVs.[15-17] Such a finding was further confirmed in a case-control study where CCSVI patients treated with venous percutaneous transluminal angioplasty (PTA) significantly improved CSF flow and velocity respect to controls.[18]

ii) The second consequence of restricted brain outflow is the reduced cerebral perfusion.[19-20] However, no data are available to understand if perfusion can be improved by vascular procedures on the IJVs.

Interestingly, either hypoperfusion of brain parenchyma or reduced CSF flow were also assessed in controls with CCSVI not associated with neurodegenerative disorders, confirming the pathophysiological role of extracranial venous abnormalities independently from concomitant neurological diseases.[16,21]

In the past we treated CCSVI with PTA with interesting results but with a dramatic rate of CCSVI recurrence, especially in case of long and not mobile valve leaflets, longitudinally disposed, and/or of muscle compression.[2,7,22] On the other hand, stenting major veins is an off label procedure, not recommended by FDA in consequence of the absence in the market of approved devices.[23] Alternatively, in cases not suitable for PTA, vascular surgeons may repair the vein by the means of an open surgical procedure consisting in endo-phlebectomy with removal of defective valves/muscular compression, complemented by patch angioplasty in autologous vein.[7,9]

In the present study we hypothesized to reduce cerebral ventricles volume and to improve brain perfusion by the means of an open surgical procedure aimed to increase the brain outflow through the jugular route. Single proton emission computed tomography (SPECT) combined with three dimensional computed tomography (3D-CT) was used to blindly assess the results of the procedure.

MATERIALS AND METHODS

Patients population

From a cohort of 56 patients (M28/F28 mean age 44±10) with Eco-Colour Doppler (ECD) with positive screening for CCSVI[24] entered the study approved by the Azienda Ospedaliera Universitaria di Ferrara Ethical Committee, and all signed an informed consent.

Inclusion criteria were:

- Age 18-65 year old
- Anatomical presence of truncular venous malformation in at least one IJV (long, not mobile leaflets in defective valves and/or intraluminal defects like septum, membrane, etc.[9]
- Restricted brain outflow through the IJV measured so agreed respectively by the means of ECD quantification protocol[13] and MRV morphological and flow evaluation protocol.[1,20]
- Diffuse hypoperfusion of brain parenchyma measured by the means of SPECT-CT
- Willing to participate to the study

Exclusion criteria were:

- Contraindications to SPECT-CT

- Contraindications to MRV
- Pregnancy
- IJV malformation not agreed between ECD quantification protocol and MRV.
- Cases suitable for PTA (short and parallel not mobile leaflets, segmental hypoplasia, flaps, etc).
- Normal brain perfusion
- Presence at cerebral MRI of intracranial vascular malformations
- Significant comorbidities in the cardiovascular, respiratory, digestive, hepatic and renal systems.
- Absence of any neurological symptom and/or associated neurological diseases
- Symptoms mainly confined to the spinal cord.

ECD flow quantification assessment

Patients were studied at baseline by the means of a validated ECD protocol of flow quantification, aimed in measuring the cerebral outflow through the main pathways, IJVs and vertebral veins (VVs), respect to the individual arterial inflow.[13] Patients were investigated in supine posture, using the recommendations regarding position, room temperature, hydration status previously approved in a consensus.[24] We assessed the presence of intraluminal obstacles/defective valves by the means of a combination of B and M-mode analysis (Fig. 1).[24] Quantification of flow was achieved by an established ECD methodology, which permits to respectively assess the head inflow (HBinF) (sum of common carotids and vertebral arteries flow) as well as the cerebral inflow (CBF) (sum of internal carotid and vertebral arteries flow). We also assessed the head outflow (HBoutF) defined as the sum of the flow rate measurements

at the jugular-subclavian junction and the VVs. In addition, we also calculated the collateral flow index (CFI) by estimating the flow which re-enters directly into the superior vena cava as the amount of blood extrapolated by the difference between the HBinF and the HBoutF.[13]

Magnetic resonance venography (MRV)

All subjects were examined on a GE 1.5T scanner. A multi-channel head and neck (HDNV) coil was used to acquire the following sequences: an unenhanced 2D-Time of Flight (TOF) and enhanced 3D-Time Resolved Imaging of Contrast KineticS (TRICKS), as previously described.[25-27] The parameters used for TOF were: TR/TE 17/4.3 msec (repetition/echo time), flip angle of 70 degrees, 1.5 mm slice thickness, field of view (FOV)=220mm, acquisition matrix 320/192, phase FOV 75%, for an in-plane resolution (IPR) of 0.7mm x 1.1mm and acquisition in axial scan plane. The parameters used for TRICKS were: TR/TE 4.2/1.6 msec, flip angle of 30 degrees, 2 mm slice thickness, FOV=340mm, acquisition matrix 320/192, phase FOV 75%, IPR = 1.1mm x 1.8mm and acquisition in coronal scan plane. Intravenous gadolinium contrast (Omniscan®, GE Healthcare, Princeton NJ) was injected at a rate of 2ml/s using a pressure injector followed by a 20ml saline flush. The total volume of contrast was 20ml. After acquisition of a 12 second mask (pre-contrast phase), the scanning of subsequent phases began simultaneously with the intravenous injection. The scan protocol consisted of 18 phases of acquisition, each of a 5 second duration.

The flow morphology, indicative of anatomical stenoses, of IJVs was assessed on axial source TOF images, as well as on axial reconstructed TRICKS images, as previously described (Fig. 2).[27] The IJV flow was evaluated on an ordinal scale ranging from absent (no visible flow) to ellipsoidal (patent lumen) and defined in 5 qualitative flow categories: absent, pinpoint,

flattened, crescentic and ellipsoidal. Only absent or pinpoint flow of the IJVs was considered to be abnormal, while the flow of the VVs was classified as absent/present

In addition, it has been recently described an aspect related to external compression, named as pencil tip sign, as a further positive criterion.[7]

SPECT-CT protocol

Cerebral perfusion evaluation

Regional cerebral blood flow (rCBF) SPECT scanning was performed 30 to 60 min following administration of 99mTc-exametazime (HMPAO, Ceretec, GE Pharma, Milwaukee, WI, USA). While lying supine with eyes closed in a dimly lit, quiet room, each subject received an intravenous injection of 740-925 MBq of 99mTc-HMPAO. Brain SPECT was performed with a dual-head SPECT-CT camera (Symbia Intevo, Siemens Healthcare, Erlangen, Germany) equipped with low-energy and high-resolution parallel-hole collimators. The head of each patient was held with fixation strips attached to a specially constructed carbon fibre head holder, which allowed the camera detector to rotate very close to the head. The data were collected into a 128 × 128 matrix, through 360° rotation at steps of 3.75° for 30 s per view (total of 96 projection). Filtered backprojection using a Butterworth and Ramp filter was used for SPECT image reconstruction.

For each patient the second study was performed after administration of the same dose (±5%), in similar conditions and acquiring images at the same time after tracer injection in comparison to first examination in order to optimize the reproducibility of the technique. [28]

Each perfusion brain SPECT study was quantified and compared to an age- and gender-matched normal database using NeuroGamTM Software package (Siemens Medical Solutions, Segami

Corporation, Columbia, MD, USA). This software applies an anatomical coregistration by blocks of data defined in the Talairach space. [29-30] Each study was reoriented according to the three-dimensional volume of the brain defining a line that fits the inferior pole of the occipital lobe and the inferior edge of the frontal lobe. Raw data were corrected for lateral deviations and defined the vertical anterior commissure line and the posterior commissure line. With this information, the Talairach technique rendered the brain volume into a normalized volume (according to the mean cerebellum rCBF value) allowing a voxel by voxel comparison of the HMPAO uptake in the brain cortex with a normal database of subjects also corrected volumetrically. For the semiquantitative analysis a predefined anatomical area template was used in order to define with high reproducibility the exact localization of areas of hypoperfusion. Perfusion was investigated for total brain, for whole cortex of both hemispheres and for frontal, temporal, parietal, occipital and cerebellar lobes bilaterally, for a total of 13 regions.

Perfusion values of cerebral areas for each patient are expressed by means of standard deviation from the values of the normal database (age and gender adjusted). Abnormal areas were defined as those with decreased uptake (below 2 standard deviations of the normal mean uptake per area >50% pixels). For comparisons we used the mean values of perfusion for each cortical area under study.

Image analysis was performed by an experienced nuclear medicine physician who was blind to the results of both clinical data and other instrumental testing.

CT measurements of ventricular volumes

At the end of each scintigraphic acquisition, patients were maintained in the same position and underwent a non contrast axial CT scan examination of the brain exploiting the multislice-CT

system integrated in the hybrid tomograph Symbia Intevo. The selected exposure factors were 130 kv and 30 mA, the slice thickness was 1.0 mm, the gantry rotation time was 0.8 s and the matrix was 512x512.

The so obtained volumetric data were transferred to a workstation with commercially available 3D reconstruction software (Syngo, Siemens AG, Berlin and München, Germany) for further processing.[31-32] Transverse slices were reconstructed with a section width of 1.0 mm. Images were processed from the obtained source data by using a volume-rendering technique algorithm, imposing a tight window including CSF mean density (from -20 to +20 H.U.). From the 3D reconstructed images of all CSF spaces, ventricular cavities were subsequently extrapolated erasing the other CSF structures through the use of regions of interest drawn manually on the volume-rendered image, obtaining for each study the value of total ventricular volumes expressed in millilitres (Fig. 3).

Surgical procedure

The surgical procedure included a monolateral or bilateral supra-clavicular transversal incision of about 5cm. The IJV was isolated at the junction with the subclavian vein. The latter was tangentially clamped following systemic injection of heparin. An endo-phlebectomy was subsequently performed with complete removal of the jugular valve/septum, followed by a patch angioplasty in autologous great saphenous vein. Omohyoid muscle section was performed if the pre-operative finding of extrinsic compression was confirmed in the surgical theatre.[6-7]

End points and Follow-up

Primary outcome measure was ventricles volume. Secondary outcome measures were brain perfusion, and 18 months patency rate.

ECD evaluation was performed at patient discharge from the Hospital, and at 15, 30 days, respectively. Subsequently, evaluation was done every 3 months. SPECT-CT was repeated at 30 days postoperatively. The same was done for controls.

Statistical analysis

Data are expressed as mean and SD. Differences in demographics, SPECT perfusion between operated group and control group, as well as between pre and post operative IJV flow and ventricles volume were analysed by Student T-Test or Mann Whitney as appropriate. Differences in IJV morphology, and in improved perfusion at follow up in operated patients and controls was compared by means of two-tailed Fisher Exact Test with determination of OR and 95% CI. Level of significance was $p<0.05$.

RESULTS

Patients population

From the initial cohort of 56 patients, 15 patients were excluded based on the inclusion/exclusion criteria listed above. Forty-one patients fulfilled the criteria and entered the study (M22/F19 mean age 48±7 yo). Twenty-seven patients constituted the surgical group, whereas 14 patients the control one. Both underwent to ECD and SPECT-CT follow up. In table I the patient population demographics are given, including proportion of relapsing remitting and secondary progressive MS patients.

ECD flow quantification assessment

The CCSVI group showed HBinF and CBF similar to that reported in literature. Outflow analysis confirmed a restricted venous flow in the IJVs respect to references values and an increased collateralization.[13] Presence of IJV valve at M-mode, number of defective not mobile valves, external compression and segmental hypoplasia in the 2 groups are given in table I. Postoperatively the HBoutF was significantly increased and CFI was found significantly reduced in the treated group, whereas not significant differences were measured in the control group. Particularly, CFI passed from 65% to 26% ($p<0.0003$). Detailed flow values and CFI among different group are shown in table II.

CT volumetry of the cerebral ventricles

Preoperatively there was not significant differences in ventricular volumes between the treated group and the control population.

The postoperative ventricular volume was significantly reduced with respect to preoperative values (from 33.5 ± 13.6 cm^3 to 31.3 ± 13.1 cm^3; $p< 0.0106$. The effect was mainly significant in patients with RR (from 27.2 ± 12.6 cm^3 to 24.6 ± 10.7 cm^3;$p=0.0098$) whereas it was not in SP group (from 39.3 ± 12.1 cm^3 to 37.5 ± 12.4 cm^3; $p=0.1834$). To the contrary in the controls we did not assess any significant change in the follow up (from 26.1 ± 14.1 to 26.7 ± 13.9, $p=0.16998$) (Fig. 4).

SPECT perfusion of the brain

In table III and in figure 5 the perfusion values of the 41 subjects respect to the Atlas of normality are given, showing a significant and diffuse hypoperfusion of the whole brain, as well

as in the other 12 segmented areas. The phenomenon was particularly pronounced in the occipital region.

By comparing in table IV the surgical group with the control group, perfusion appears improved in the former, reaching the level of significance respect to control population in left and right occipital regions (Fig. 6). Again the effect is more dramatic in the RR subgroup with increased level of significance either in the occipital and in parietal regions. To the contrary, again in the SP population the surgical procedure did not achieve any significant improvement of cerebral perfusion.

Surgical Outcomes

We performed 40 surgical procedures on the IJVs, 15 were performed bilaterally; omohyoid muscular section was performed in 20 cases, confirming the high prevalence of the extrinsic compression in CCSVI. The Hospital stay was on average 5.0±1.5 days out of one case who reported a thoracic duct injury. This complication was managed in hospital for additional 2 weeks. There was no mortality but a considerable complication rate was registered and given in details in table 5.

On the other hand, the patency rate was quite satisfactory 73% at 18 months (Figure 7)

DISCUSSION

CSF is formed through ultrafiltration in the capillary of the lateral ventricles of the brain. CSF is absorbed into the intracranial venous system through a physical mechanism driven by a gradient of pressure. It is required a gradient at least of 5 mmHg to allow passage of the fluid from sub-arachnoid spaces to the sinusal veins. Moreover, the rate of CSF clearance was calculated be 0.1031mL/min/mmHg.[33] A correct balance between ultra-filtration of CSF and its clearance from the CSF space into the dural veins, is clearly dependent on efficient venous drainage.[34-35]

Recent computational studies mimicking the presence of a not mobile and closed valve in the IJV,[36] or a restricted jugular flow in consequence of any kind of mechanism stenosing the vein,[35] calculated a consequent increased pressure in the dural veins. Particularly, in the dural sinuses, when both IJVs are obstructed, it has been calculated a rise in pressure up to 13 mmHg.[35] This calculation tells us why jugular surgery, by reducing the venous pressure,[2] in turn acts favorably on the CSF absorption into the venous system.[18] Impaired CSF circulation in presence of jugular flow abnormalities is a finding described in several neurodegenerative diseases like Alzheimer,[37] multiple sclerosis,[17-18] Parkinson,[38] and Meniere disease,[39] where in all seems to increase lesions in the white matter and/or the predisposition to the associated neurological disorder.

Our findings support that jugular valve obstacle is a contributing factor to the enlargement of 3rd and lateral ventricle volumes that we measured (Fig. 4), very frequently observed in MS patients. It is usually considered an indirect index of brain atrophy.[40-41] Ventricular volume correlates with clinical disability and neuropsychological assessment in MS patients.[40] In a cohort of patients with early MS, third ventricular enlargement was a powerful predictor of motor deficits and cognitive impairment.[41] In the present study, in MS patients with concomitant CCSVI this parameter was improved by surgical repair of the IJVs. However, by subsetting our population

respectively in RR and SP cases, the positive effect was registered only in the former, characterized by a shorter duration of the disease with less severe clinical consequences (Fig.4). As far as the secondary outcome measures are concerned, in our patient cohort we assessed at bottom line, as expected, a significant reduction in perfusion, a well known vascular aspect in MS and in other neurodegenerative disorders.[19-21,42] Moreover, it has been recently shown how perfusion of the brain is also correlated to the jugular flow.[20] To the best of our knowledge this is the first study demonstrating improved brain perfusion following flow restoration in the cerebral draining veins. In MS any treatment addressed to improve cerebral perfusion should be taken into consideration because:

i) Plaques formation is preceded by low perfusion.[43]

ii) The reparative process is more efficient in brain areas with adequate perfusion. It has been demonstrated in patients with better SPECT perfusion an improved chance to re-myelination and to brain tissue reparative process.[44]

A trend in decreased plaques formation following venous PTA was demonstrated in a case control study, confirming the need of investigating rate of plaques formation in properly designed randomized study.[45]

Open surgery in this particular moment demonstrated to be a valid alternative to off label stenting, because the registered 18 months patency rate is certainly better respect to that reported in PTA studies.[2,22] However, of course, the morbidity was quite increased. Particularly, blood and lymph collection was the more common complication. This required always a treatment because in upright the hydrostatic pressure of the IJV is negative, and fluid collection may contribute to significant compression, potentially affecting the patency rate. Treatment can be an echo-guided puncture or a redo surgery. In our series when we omitted treatment due to a clinical

evaluation of possible spontaneous absorption, the result was the subsequent occlusion of the vein.

Collectively, our findings demonstrate that CCSVI has a significant impact on brain patho-physiology, and particularly on the balance of intracranial fluids. Our study demonstrates that this effect can be achieved limitedly to early cases, whereas it is not expected the same affects in patients with progressive clinical course and longer duration of the disease. The same was observed by the assessment of cerebral perfusion.

Someone may argue that a potential limitation of the study is to consider the ventricular cavity volumes as the expression of the whole CSF volume. Our CT calculation does not take into account, for structural complexity reasons, the subarachnoid spaces. However, since they are structures extensively communicating with each other, there is no reason to believe that a volumetric reduction in brain ventricles is not associated with a decrease in the overall amount of CSF. In particular, as shown by the images B and E in figure 3, it is possible to visually appreciate, between before and after surgery, a significant reduction of the subarachnoid spaces component (in light purple) that goes hand in hand with the lowering in size of ventricular cavities (in purple).

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In conclusion, when the extracranial venous drainage is hampered, our study shows an overlooked mechanistic component in the pathophysiology driven the enlargement of cerebral ventricles, as well as a role of the flow among the factors influencing brain perfusion. When venous surgery is applied in early stages may improve both aspects, common to several neurodegenerative disorders.

We hope our study could provide stimulation for the development of dedicated devices for a safe and effective endovascular treatment of intraluminal obstacle and/or extrinsic jugular compression

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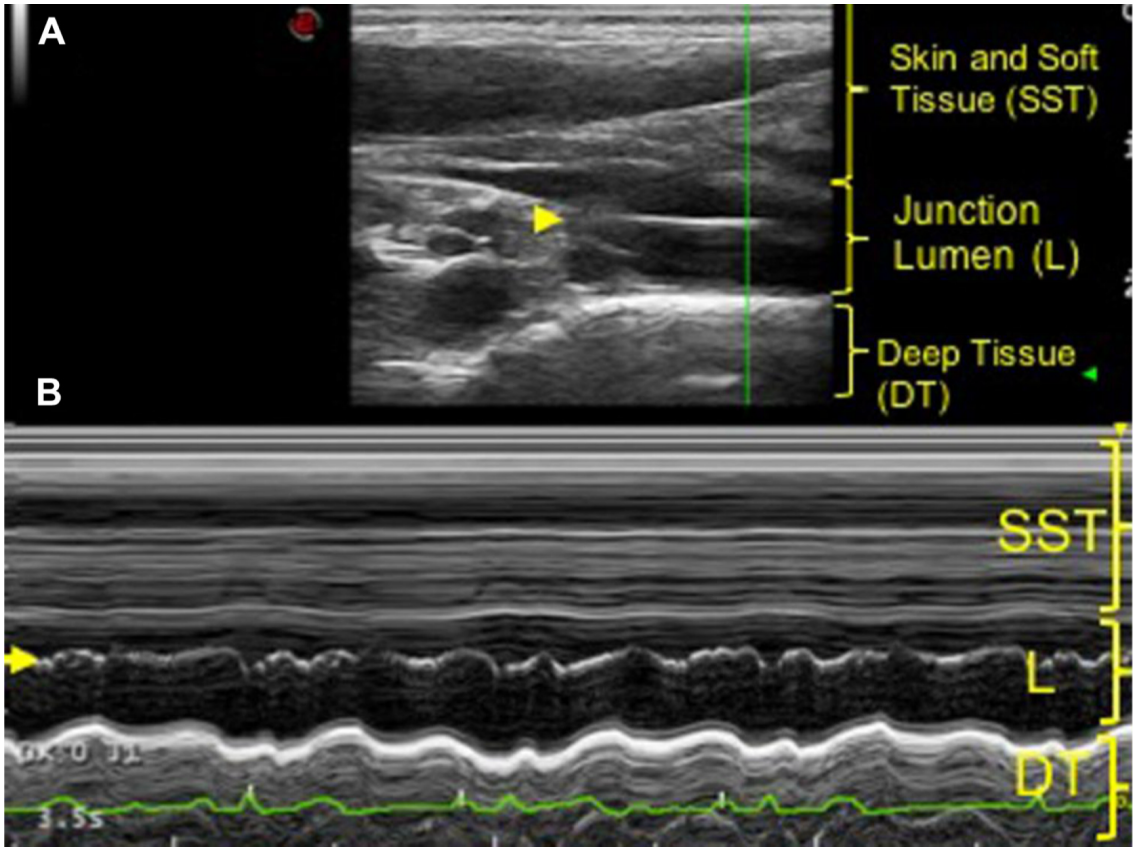

Fig 1. A, B-mode image showing the different layers; the arrowhead indicates the monocusp jugular valve. B, The M-mode analysis demonstrates the immobility of the monocusp in any postural and respiratory condition. The arrow indicates how the cusp is a fixed intraluminal obstacle. In the deep tissue, the electrocardiography trace is depicted. It shows the absence of valve opening in any phase of the cardiac cycle.

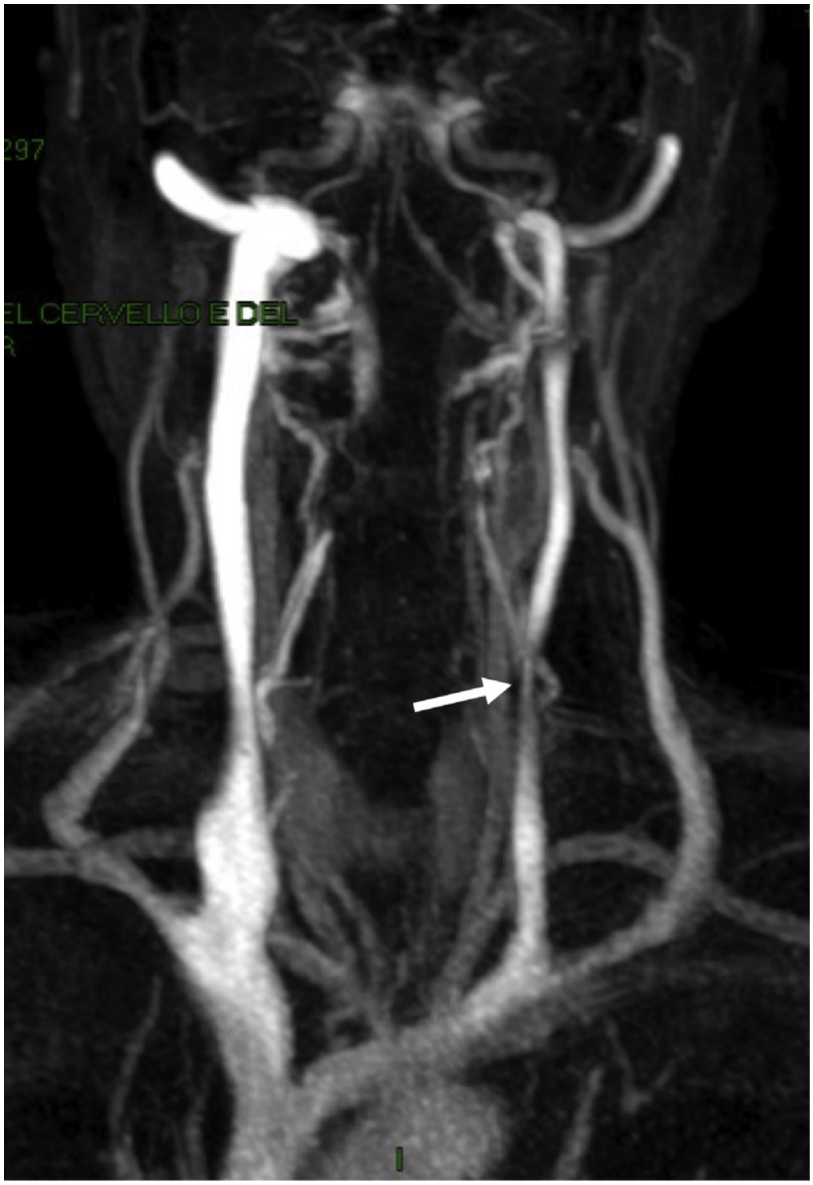

Fig 2. Magnetic resonance venography (MRV) of the extracranial venous system. The arrow shows a stenotic left internal jugular vein (IJV) in consequence of omohyoid muscle compression, compensated by an enlarged external jugular vein. The pencil tip sign is readily apparent.

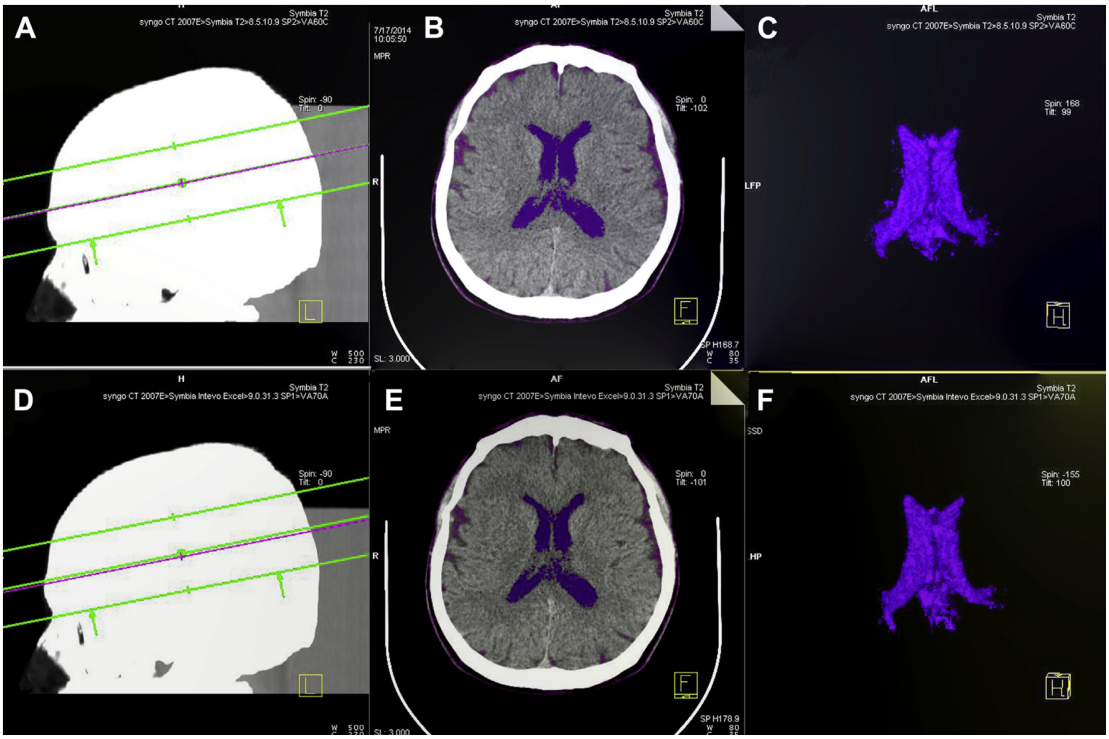

Fig 3. In the top and bottom are displayed images, respectively, related to presurgical and postsurgical computed tomography (CT) acquisition. A and D, Lateral scout view of the skull showing the interval of three-dimensional CT reconstruction. B and E, Middle cerebral CT slice that highlights ventricles (in purple) and subarachnoid spaces (in light purple). C and F, Three-dimensional rendering reconstruction of the ventricular cavities. The significant reduction in size of the ventricular spaces between the study performed before surgery (C) and the one acquired at 1 month from endophlebectomy (F) is apparent.

Table I. Demographics and clinical characteristics of the two cohorts

	Surgical group (n ¼ 27)	Control group (n ¼ 14)	P
Age, years	48 ± 7	44 ± 11	.47
Gender	14 M, 13 F	8 M, 6 F	.74
MS clinical class	13 RR 14 SP	8 RR 6 SP	.74
RR disease duration, years	10 ± 4	9 ± 3	.55
SP disease duration, years	13 ± 4	14 ± 1	.29
M-mode valve presence	40/54 (74%)	22/28 (78%)	.79
Defective valves	40/54 (74%)	22/28 (78%)	.79
Compression	20/27 (74%)	6/14 (42%)	.15
Jugular hypoplasia	2/27 (7%)	0/14 (0%)	.54

MS, Multiple sclerosis; RR, relapsing remitting; SP, secondary progressive.

Table II. Flow values and collateral flow index (CFI) among different groups

	Surgical group, preoperative (n ¼ 27)	Surgical group, postoperative (n ¼ 27)	P	Control group, preoperative (n ¼ 14)	Control group, postoperative (n ¼ 14)	P
HBinF, mL/min	970 ± 220[a]	920 ± 150	.35	900 ± 150	900 ± 80	.87
CBF, mL/min	610 ± 180[a]	600 ± 110	.97	530 ± 100	530 ± 70	.61
HBoutF, mL/min	320 ± 200[a]	740 ± 280	**<.0008**	580 ± 240	520 ± 170[a]	.37
CFI	70 ± 20[a]	30 ± 20	<.0003	40 ± 30	40 ± 20[a]	.60

CBF, Cerebral blood inflow; HBinF, head blood inflow; HBoutF, head blood outflow.

The boldface P values indicate that both postoperative HBoutF and CFI were significant improved in the surgical group.

[a]No statistical differences in preoperative inflow and outflow values between surgical and control groups (P ¼ .16; P ¼ .09; P ¼ .07; P ¼ .11).

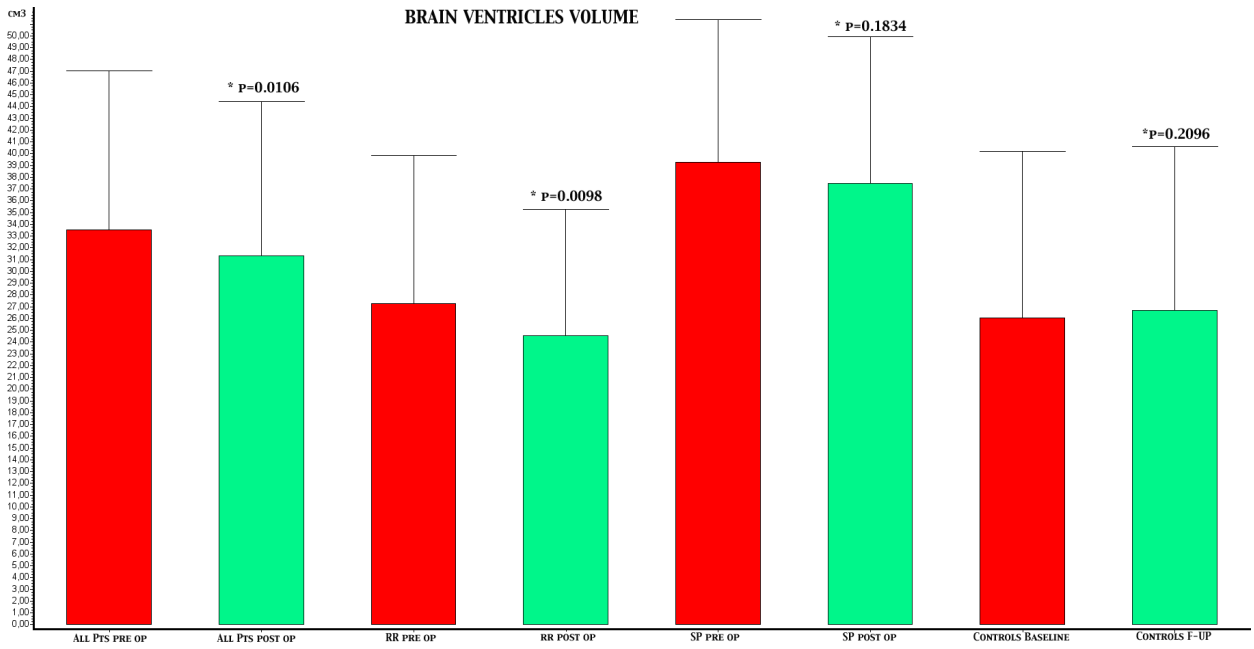

Fig 4. Four pairs of histograms comparing preoperative (PRE OP) and postoperative (POST OP) values of ventricular volume in the treated group, which was significantly reduced. By stratifying the relapsing remitting (RR) patients, the reduction was even much more significant (second pair). To the contrary, in the secondary progressive (SP) subset, the difference was not significant (third pair). Finally, the fluctuation of ventricular volume in the control population did not change significantly. F-up, Follow-up; PTS, patients.

Table III. The preoperative perfusion values in controls, in whole population of patients, and in relapsing remitting (RR) and secondary progressive (SP) subgroups

	Controls	All patients	P	RR group	P	SP group	P
Entire brain	-1.6 ± 1.2	-1.9 ± 0.8	.29	-1.9 ± 0.7	.42	-1.9 ± 0.9	.38
Cortex	-1.6 ± 1.3	-1.8 ± 1.0	.29	-1.7 ± 1.0	.46	-1.9 ± 1.0	.19
Frontal	-1.8 ± 1.5	-2.0 ± 0.9	.18	-1.9 ± 0.9	.47	-2.1 ± 1.0	.17
Temporal	-2.1 ± 1.5	-2.2 ± 1.1	.56	-2.1 ± 1.0	.89	-2.3 ± 1.1	.43
Parietal	-1.2 ± 1.2	-1.6 ± 0.8	.12	-1.6 ± 0.7	.19	-1.7 ± 1.0	.17
Occipital	-0.7 ± 1.2	-1.2 ± 0.9	**<.03**	-1.2 ± 0.7	.05	-1.0 ± 1.0	.30
Cerebellum	-1.4 ± 0.8	-1.2 ± 0.8	.58	-1.2 ± 0.7	.05	-1.1 ± 0.8	.40

Data are given in units with respect to the atlas of normality. P is referred to controls. The boldface P value indicates a significantly better occipital perfusion in controls.

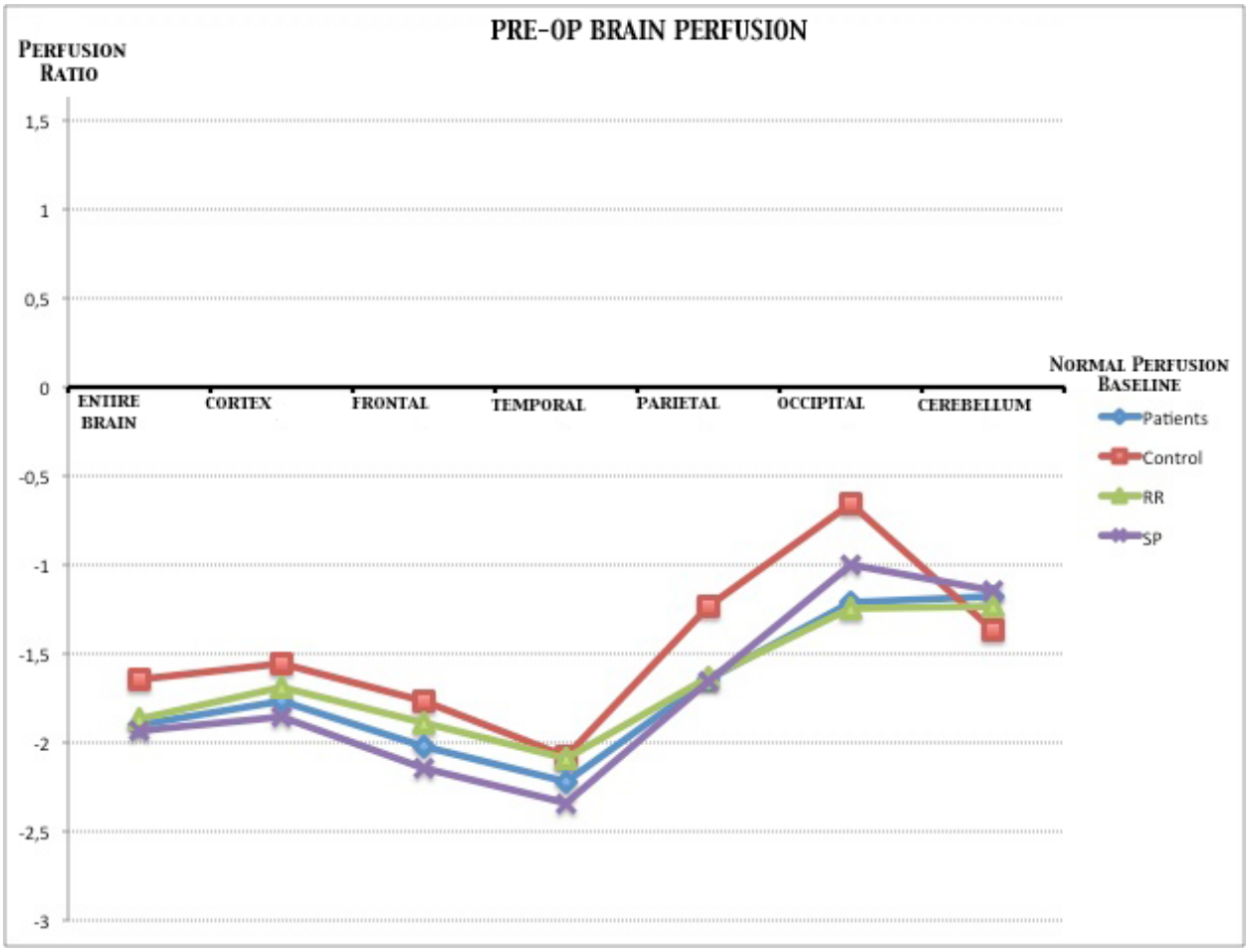

Fig 5. Brain perfusion values in the entire brain and in the 12 evaluated areas with respect to the atlas of normality in all patients, controls, and relapsing remitting (RR) and secondary progressive (SP) patients. Cortex, frontal, temporal, parietal, occipital, and cerebellar regions display the sum of the left and right perfusion. All the groups were below normal perfusion (0 line).

Table IV. Postoperative perfusion values in controls, in whole population of patients, and in relapsing remitting (RR) and secondary progressive (SP) subgroups

	Controls	All patients	P	RR group	P	SP group	P
Entire brain	0.4 ± 1.8	0.6 ± 2.0	.94	1.4 ± 2.0	.47	-0.1 ± 1.8	.60
Cortex	0.1 ± 1.8	0.5 ± 2.2	.63	1.1 ± 2.1	.17	-0.1 ± 2.1	.70
Frontal	0.6 ± 1.9	0.3 ± 2.3	.54	0.9 ± 2.2	.83	-0.2 ± 2.2	.23
Temporal	0.5 ± 2.4	0.6 ± 2.5	.44	1.3 ± 2.5	.81	-0.1 ± 2.2	.13
Parietal	-0.2 ± 2.1	0.9 ± 2.4	.11	1.7 ± 2.1	**<.02**	0.1 ± 2.4	.61
Occipital	-0.8 ± 2.1	1.3 ± 2.1	**<.0003**	2.2 ± 2.0	**<.0001**	0.5 ± 1.9	.05
Cerebellum	0.6 ± 2.4	0.8 ± 2.3	.49	1.2 ± 2.3	.35	0.4 ± 2.3	.75

P is referred to controls. The boldface P values indicate a postoperative significantly improved perfusion respectively in the parietal and occipital regions of the RR group and in the occipital area of whole operated patients.

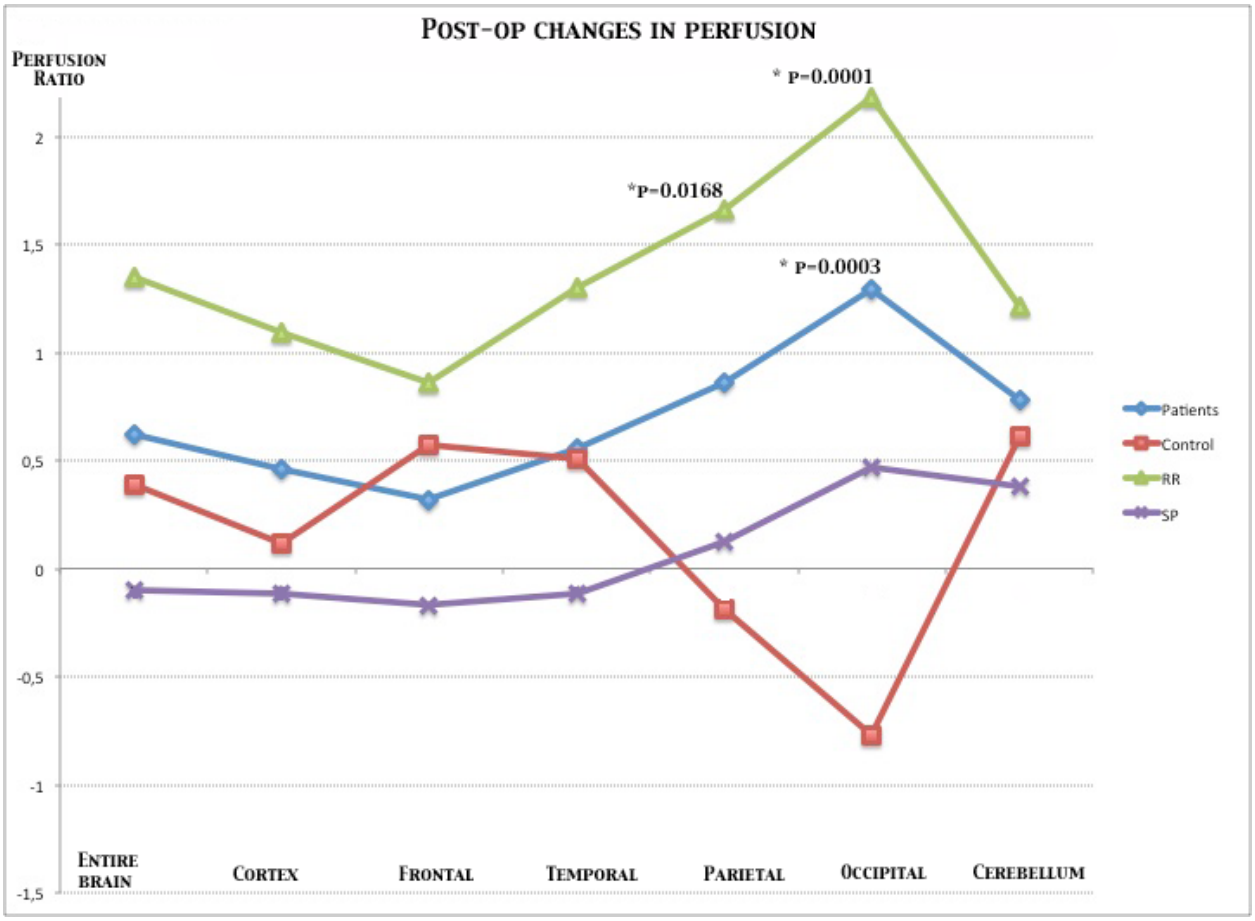

Fig 6. Postoperative perfusion values measured in the entire brain and in the 12 evaluated areas. The green line refers to the relapsing remitting (RR) group of patients, who significantly improved perfusion with respect to controls (red line), with significant changes in both the occipital and parietal lobes. To the contrary, the secondary progressive (SP) group of patients (violet line) did not significantly improve. The blue line indicates the postoperative improvement of the whole surgical population.

Table V. Complication rate

Complication type	No. (%)
Hematoma	4/27 (15)
Thoracic duct injury	1/27 (4)
Bleeding	1/27 (4)
Cranial nerve injury	1/27 (4)

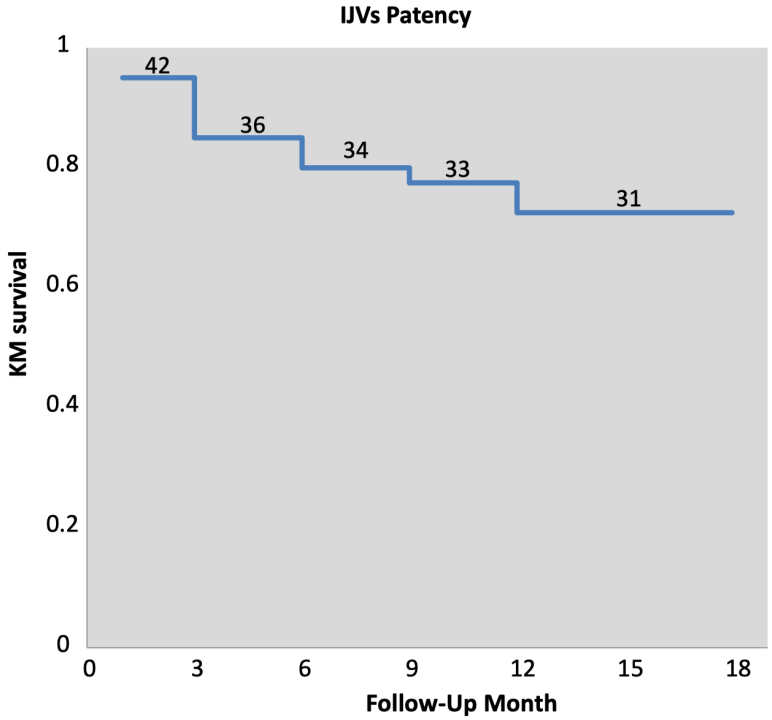

Fig 7. Kaplan-Meier (KM) curve estimation of the patency of the internal jugular veins (IJVs) at 18 months of mean follow-up. The number of patent IJVs is reported on each major time interval.