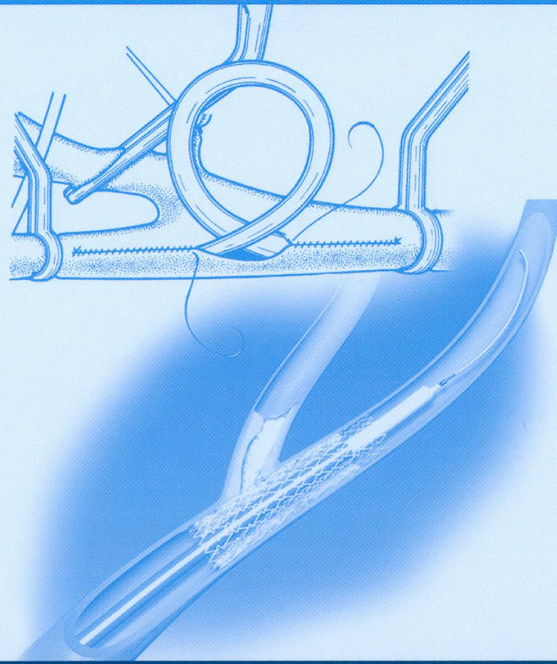


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1978–2009
31 YEARS

Vascular and Endovascular Controversies Update



Roger M Greenhalgh



BIBA Publishing
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Published by
BIBA Publishing
A division of BIBA Medical Ltd

BIBA Medical, 44 Burlington Road, London SW6 4NX, UK

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First Published 2009

ISBN: 0-9544687-6-7

British Library Cataloguing in Publication Data
A catalogue reserved for this book is available from the British Library

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Managing Editor on behalf of BIBA Medical:
Naughton Project Management, Unit 2.10,
Medway Enterprise Centre, Enterprise Close,
Medway City Estate, Rochester, Kent, UK

Typeset by Phoenix Photosetting, Chatham, Kent, UK
Printed and bound by MPG Books Ltd, Bodmin, Cornwall, UK

Rationale and preliminary results of endovascular treatment of multiple sclerosis, the liberation procedure

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Introduction

Multiple sclerosis is an inflammatory, demyelinating disease of the central nervous system of unknown pathogenesis; it is considered to be autoimmune in nature.¹⁻² It is the most common disease causing disability in young people. The clinical course is usually classified as *relapsing remitting* (characterized by acute exacerbations of the disease followed by complete or partial recovery), *secondary progressive* (characterized by progressive deterioration of neurologic function after several years of relapsing remitting course), and *primary progressive* (characterized by a progressive clinical course starting from the beginning).³

Magnetic resonance venography⁴⁻⁷ and postmortem studies⁸ demonstrated a topographic correspondence between multiple sclerosis plaques and the cerebral venous system. Histologic examination of the involved veins reveals unequivocally the presence of characteristic signs of impaired venous drainage, such as perivenous iron deposits and fibrin cuffs, particular to chronic venous insufficiency.⁹

All of these elements convinced the current authors to investigate Doppler cerebral venous hemodynamics.¹⁰ Cerebrospinal venous return in multiple sclerosis patients was found to be anomalous with respect to controls (including healthy subjects matched for age and gender, patients affected by other neurologic diseases, and healthy subjects older than the median age of onset of multiple sclerosis).¹¹⁻¹³ Venous hemodynamics was investigated by combining extracranial echo-colour-Doppler of the internal jugular veins – vertebral veins. Trans-cranial colour-Doppler sonography was used for studying the deep cerebral veins, focusing on the detection of five anomalous parameters, which are absent in normal subjects (Table 1).¹⁰

Sensitivity, specificity, positive predictive value and negative predictive value were tested for significance by the two-sided Fisher exact test, by comparing the gold standard diagnostic assessment, represented by clinical and magnetic resonance imaging revised McDonald criteria for diagnosis of multiple sclerosis, with the proposed echo-colour-Doppler-trans-cranial colour-Doppler sonography protocol.

Table 1. Echo-colour-Doppler-trans-cranial colour-Doppler sonography parameters of abnormal cerebral venous outflow in multiple sclerosis

Echo-colour-Doppler-trans-cranial colour-Doppler sonography parameters	Multiple sclerosis (%)	Control populations (%)	Sensitivity Specificity Positive predictive value-Negative predictive value (95% CI)	<i>p</i>
1. Spontaneous reflux constantly present in the internal jugular veins and/or vertebral veins in both sitting and supine posture	70%	0%	100% (95-100) 84% (79-89) 70% (60-78) 100% (98-100)	< 0.0001
2. Reflux propagated upward to the deep cerebral veins	50%	0%	100% (93-100) 77% (71-82) 50% (41-60) 100% (98-100)	< 0.0001
3. High resolution Bmode evidence of proximal internal jugular vein stenoses	28%	0.6%	97% (83-99) 69% (63-75) 28% (19-37) 99% (97-100)	< 0.0001
4. Flow not Doppler detectable in the internal jugular veins and/or vertebral veins despite numerous deep inspirations	32%	0.6%	97% (85-99) 70% (64-76) 32% (23-42) 99% (97-100)	< 0.0001
5. IJV cross-sectional area in sitting posture > than in supine posture	58%	12%	74% (63-83) 76% (70-82) 56% (46-65) 88% (82-92)	< 0.0001
Conclusive Analysis	100%	0%	100%	< 0.0001
Two or more Echo-colour-Doppler-trans-cranial colour-Doppler sonography positive parameters			100% 100% 100% 100%	

Venography and 'intent to treat' procedures

Diagnosis of suspicious abnormal extracranial cerebral venous outflow must fulfil at least two of the five criteria listed in Table 1 and is taken as an indication approved by the Ethical Committee of the current authors' hospital to continue the study using selective venography in all suspected subjects.¹²

Selective venography demonstrates that anomalies in Doppler venous hemodynamics are due to multiple significant extracranial venous stenosis, localized at the cervical, thoracic, and less commonly abdominal level of the principal cerebrospinal venous segments. In a further control population with negative ultrasound results, which includes subjects not affected by neurologic diseases who underwent venography for other reasons, stenotic patterns were never demonstrated in the internal jugular veins, azygous, and lumbar territory.¹² In particular, the azygous vein in the multiple sclerosis group was affected in 86% of cases. Most cases involved membranous obstructions

of the junction with the superior vena cava, or, less frequently, twisting, septums and atresias as can be seen in the x-rays in Figure 1.

In 12 cases, the azygous system presented stenoses at several points up to even atresia or agenesis of the lumbar plexuses (18%). As for the jugular veins, they were found to be stenosed unilaterally or bilaterally in 59 out of 65 cases (91%). The stenoses were frequently annulus (Fig. 2) and septum, followed by atresias, and rarely by ageneses; no twisting was observed, sometimes coexistent valvular anomalies and bone compression were also observed. Interestingly, the distribution of the extracranial venous stenoses significantly influences the clinical course as well as the onset of symptoms.¹¹

Selective phlebography enabled the current authors to perform a first treatment of the identified venous obstructive lesion at the time of the diagnostic evaluation by the means of balloon angioplasty, the so called liberation procedure. Twisting of the azygous vein in nonresponders has been subsequently treated by stent insertion.

Intent to treat procedures at the time of diagnostic phlebography was performed in 77 consecutive cases. The ethical committee approved this study in February 2007.

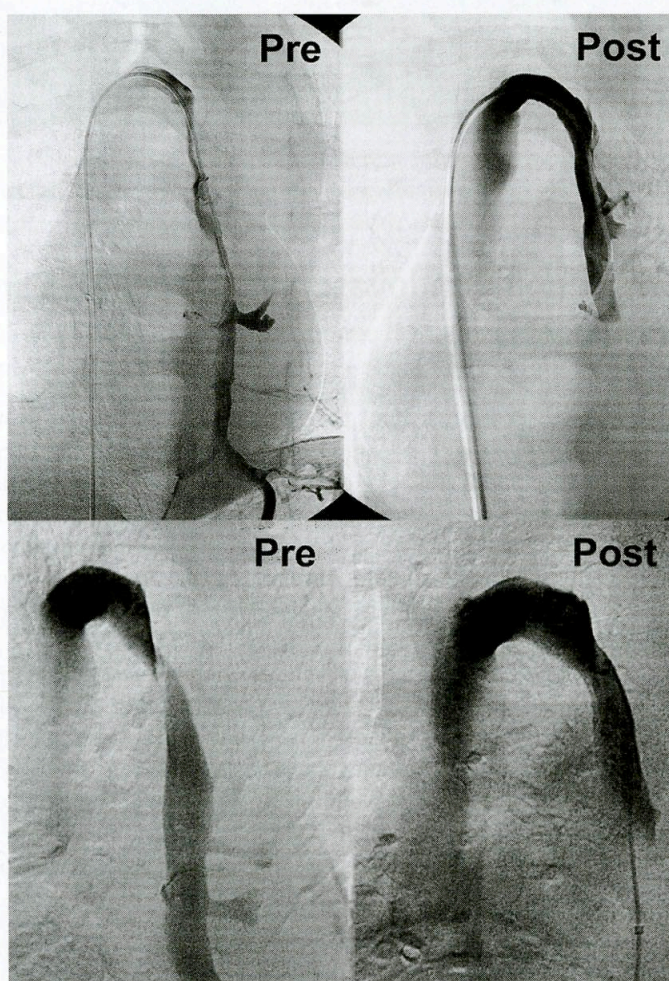


Figure 1. (Top left) Preoperative venography of the azygous vein affected by combination of membranous obstruction of the outlet into the superior vena cava and proximal atresia, with reflux extended downward to the emiazygous vein. (Top right) Postoperative result with reflux disappearance. (Bottom left) Preoperative venography of azygous vein affected by twisting. (Bottom right) Postoperative result after angioplasty.

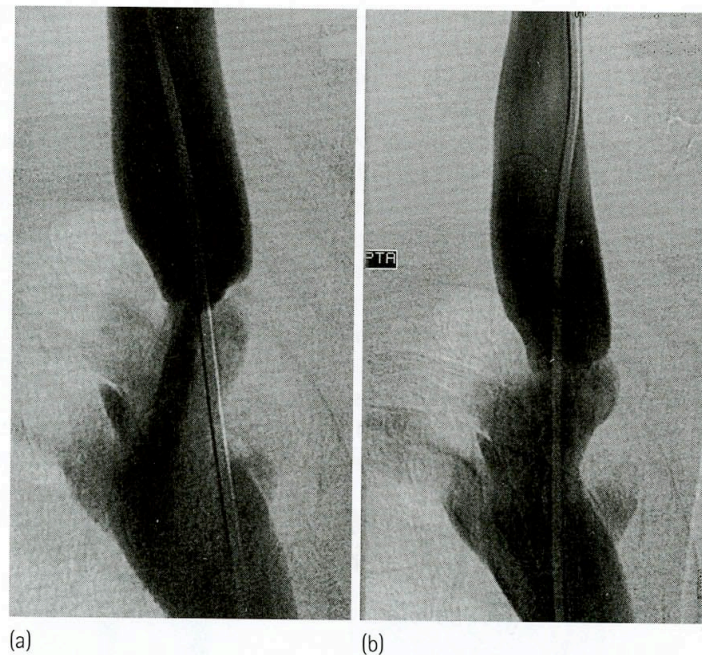


Figure 2. (a) Closed stenosis of the internal jugular vein. (b) The same case after balloon angioplasty.

Results of venous endovascular procedures in multiple sclerosis

All procedures were performed in day hospital and under local anesthesia. The procedure was well tolerated. Post-procedural observation was carried out at 4 hours and the patients were discharged with a compressive dressing on the left femoral vein, the preferred site of vascular access. The dressing could be removed the day after the procedure. A prophylactic dose of low-molecular-weight heparin is strongly recommended for the subsequent 3 weeks.¹⁴ No operative and postoperative complications were registered, including vessel rupture, thrombosis, or side effects caused by the contrast media. Minor hemorrhages with hematomas in the site of vascular access were occasionally seen.

Patients who underwent a cerebrospinal venous endovascular procedure were followed up by means of a validated clinical test for investigating the motility of upper and lower extremities as well as the cognitive function (the so-called multiple sclerosis functional composite MSFC), the expanded disability status scale, EDSS, and a recognized QoL questionnaire MSQoL-54, in addition to clinical and magnetic resonance imaging measure.^{15,16,18-20}

The venous patency and its relationship with the clinical course was also evaluated.

Clinical results

Acute attack in relapsing remitting patients

About 85% of multiple sclerosis cases begin with relapsing remitting disease; this evolves through recurrent exacerbations with subsequent full or partial recovery

before entering the progressive phase, in which any recovery of function is rare. Relapse events average about 1.1 per year early in the disease course.²¹

Relapse in the relapsing remitting clinical course is unpredictable and clinically manifests with the impairment of one or more neurologic functions. Acute attacks are usually managed with high-dose corticosteroids for 5 days. Relapse is associated with magnetic resonance imaging evidence of inflammation.

In Emergency, 18 consecutive patients were treated without use of corticosteroids, using the endovascular techniques described earlier. A total recovery time ranging from 4 hours to 4 days from endovascular treatment was observed. This was the best evidence that venous obstructions play a causative role in the complex pathogenesis of multiple sclerosis. This group of patients was followed up together with the other patients of the relapsing remitting group treated electively. Outcome measures will be described next.

Preliminary results in relapsing remitting patients

A total of 51 patients were treated with the relapsing remitting clinical course, 18 in Emergency for acute attack as described earlier, and 33 electively. Moreover 13 and 11 patients were treated, respectively, with secondary progressive and primary progressive clinical courses. This chapter herein refers exclusively to results obtained on the relapsing remitting patients. The outcome measures are those usually utilized in clinical trials evaluating multiple sclerosis treatment:

- Rate of relapse in the year subsequent to the endovascular procedure as compared to the rate registered in the same population in the preceding year (Fig. 3). The probability of acute attack decreased more than 4-fold after the endovascular treatment, OR = 4.4 (95% CI 1.5–13, $p = 0.0072$);
- MSFC Z-score, expressing the score of lower limb motility, plus upper limb motility, plus cognitive performance.^{15–16} It was significantly improved 1 and 6 months postoperatively as can be easily seen in Figure 4;

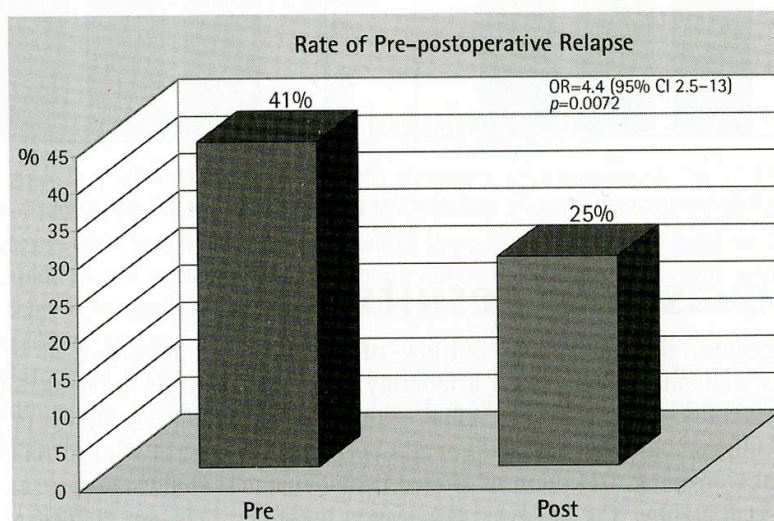


Figure 3. Significant reduction of the relapse rate in the first year after venous balloon angioplasty.

- QoL, by using a validated 54-item questionnaire focused on multiple sclerosis.¹⁸ The score was significantly increased by about 30%, as shown in Figure 5, in the composite parts concerning physical and mental status. QoL improvement is confirmed by the dramatic improvement registered in chronic fatigue. The latter aspect was also measured separately, registering a reduction of 50% on the validated fatigue scale¹⁷ ($p < 0.01$). It is stressed that chronic fatigue is one of the more disabling symptoms in multiple sclerosis, and is actually orphan of any effective treatment;
- A follow-up MRI has not been carried out.

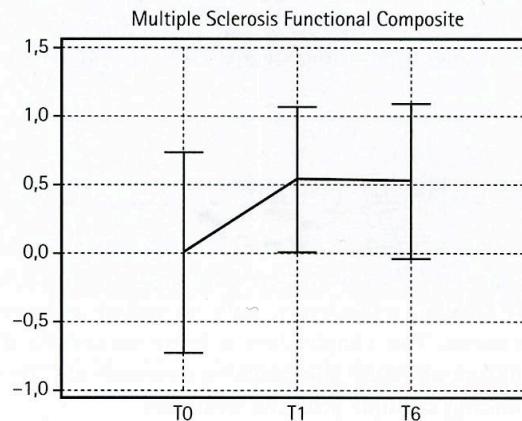


Figure 4. Z-score mean \pm SD of the multiple sclerosis functional composite at baseline and after the endovascular procedure ($p < 0.05$).

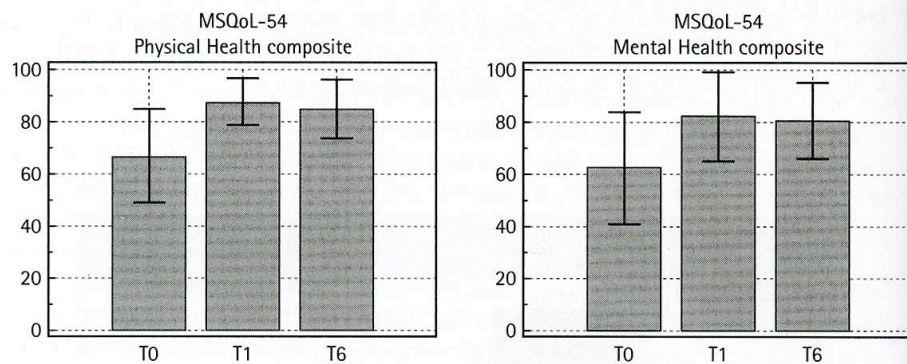


Figure 5. QoL improvement after the endovascular procedure (mean \pm SD, $p < 0.05$).

Endovascular results

Post-procedural cerebral venous outflow surveillance was performed at 1, 3, and 6 months, and subsequently on a 6-monthly basis, by means of the detection of the same echo-colour-Doppler-trans-cranial colour-Doppler parameters shown in Table 1. Vascular ultrasonography was additionally performed in case of clinical relapse and/or clinical worsening. Detection of altered hemodynamics would represent an indication for venography. The endovascular results presented here are divided according to venous segment.

Procedures on azygous vein

Membranous obstruction of the outlet of the azygous vein into the superior vena cava can be successfully managed by simple balloon dilatation. This procedure was performed in 38 out of 77 cases, and no recurrence was recorded at 1 year. Twisting of the azygous vein was observed in seven out of 77 cases that were also treated by balloon angioplasty. The latter recurred in two cases (29%), which were subsequently treated by stent insertion with a 6-month patency (Fig. 6). The same anti-platelet protocol is used in balloon angioplasty and stenting at the level of the coronary artery, in addition to administration of low-molecular-weight heparin²³.

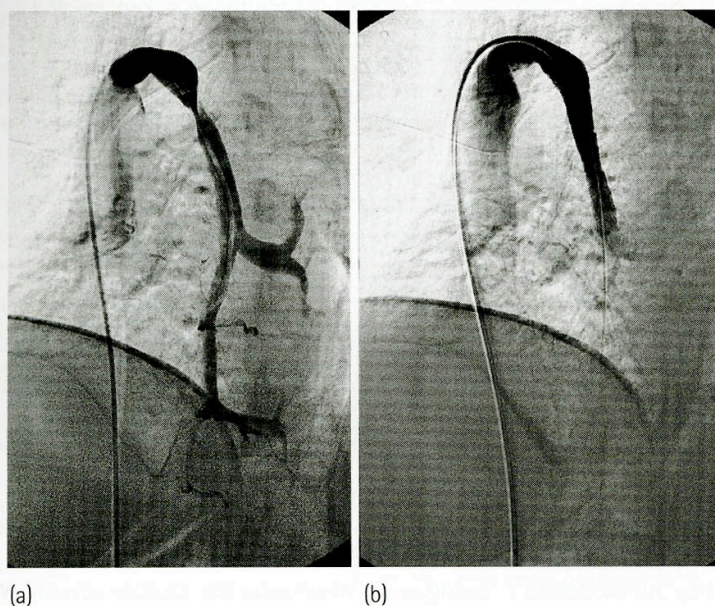


Figure 6. (a) Twisting of the azygous vein not responding to simple balloon angioplasty, causing reflux downward and inward to the spinal cord. (b) Successful stent insertion at the azygous arch with elimination of twisted stenosis and reflux.

Procedures on internal jugular veins

In contrast, overall internal jugular vein stenoses were present in 94 of 144 patients and internal jugular vein patency was achieved at 1 year in 66 of 94 patients (70%). All patients with restenosis corresponded to those who manifested relapses in the year subsequent to the endovascular treatment (Fig. 3). Symptomatic and asymptomatic restenoses were again treated with balloon dilatation. However, no attempt at a stenting procedure was made in the absence of a dedicated device capable of preventing migration. This device would fit the particular morphology of the internal jugular vein, similar to a upside down milk bottle, and, finally avoid protrusion into the brachiocephalic trunk.

Summary

- Multiple sclerosis is an inflammatory demyelinating disease of the central nervous system of unknown pathogenesis. It is considered to be autoimmune in nature and is the most common disease causing disability in young people.
- In multiple sclerosis the plaques are venocentric, with some histologic aspects particular to chronic venous disease. The Doppler hemodynamics of cerebrospinal venous return in multiple sclerosis patients is consistently altered.
- Investigation of multiple sclerosis patients with Doppler anomalies of cerebral venous return by means of venography demonstrates multiple stenoses, affecting the principal extracranial venous segments at the thoracic, cervical and sometimes abdominal level.
- The majority of venous stenoses are treatable at the time of venography with conventional, minimally invasive, and safe endovascular techniques, the so called liberation procedure.
- Endovascular treatment, with the limitation of a short follow up, improves significantly the validated outcome measure in multiple sclerosis, including the multiple sclerosis functional compositum score and QoL assessment. In addition, it reduces by more than four times the relapse rate in the year subsequent to the procedure, as compared to the preceding year.
- Treatment of the azygous vein and of the jugular vein showed a 1-year patency of 95% and 70%, respectively.

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