

CASE REPORTS

Chronic cerebrospinal venous insufficiency: report of transcranial magnetic stimulation follow-up study in a patient with multiple sclerosis

R. PLASMATI¹, F. PASTORELLI¹, N. FINI¹, F. SALVI¹, R. GALEOTTI², P. ZAMBONI²

¹Department of Neurology, Bellaria Hospital, Bologna, Italy

²Vascular Diseases Centre, University of Ferrara, Italy

The pyramidal pathway is frequently affected early on in multiple sclerosis (MS) and impaired motor performance is a major cause of disability. Pyramidal tract function can be assessed using transcranial magnetic stimulation (TMS). TMS supports the diagnosis of MS, detecting corticospinal tract involvement and monitoring its course with or without treatment. It has been never investigated whether any relationship exists between the TMS outcome measure and minimally invasive treatment of multiple severe extracranial stenosis, affecting the principal cerebrospinal venous segments in MS patients. We report the clinical and transcranial magnetic stimulation follow-up of a patient during a relapse in relapsing-remitting MS. She underwent percutaneous balloon angioplasty of the associated chronic cerebrospinal venous insufficiency (CCSVI), due to membranous obstruction of the proximal azygous vein, with severe stenosis of the left internal jugular vein. Treatment of the associated CCSVI made a parallel improvement in both clinical and neurophysiological parameters, allowing us to avoid high dose steroid therapy. The relationship between the clinical and neurophysiological course on the one hand, and haemodynamic correction of the associated CCSVI on the other, calls for further exploration on a wider number of patients. The impact of CCSVI on the different neuro-physiological parameters has not been fully estimated, but the intriguing case here reported suggests that it may be greater than previously assumed. The demonstration of a modification of the cerebrovenous function with both clinical manifestation and via TMS suggests that the hampered cerebral venous return may contribute to the clinical course of MS.

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Transcranial magnetic stimulation (TMS) supports the diagnosis of MS, detecting corticospinal

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tract involvement and monitoring its course with or without treatment.¹⁻⁴

Recent studies^{5,6} have reported the presence of multiple severe extracranial stenosis affecting the principal cerebrospinal venous segments in MS patients, leading to a picture of chronic cerebrospinal venous insufficiency (CCSVI) which is strongly associated with MS and influences its clinical course.

We report the results of TMS follow-up in a patient suffering from relapsing-remitting MS (RR-MS) with associated CCSVI, who underwent percutaneous balloon angioplasty (PTA) for severe extracranial venous stenosis.

Case report

The patient was a 28 year-old Italian woman. At the age of 22 she presented left side hypoesthesia and left optic neuritis. She was treated with high dose e.v. methylprednisolone with partial recovery. The first relapse occurred one year later with right side hypo-dysaesthesia and urinary urgency. A diagnosis of MS was performed according to clinical, neurophysiological and neuro-imaging data. A CSF study showed oligoclonal bands.

From the age of 23 to 28 she had two more relapses with bilateral motor-sensory symptoms, treated with repeated high dose e.v. methylprednisolone; from the age of 26 she started immunomodulating therapy with interferon beta 1a⁴⁴.

At the age of 28 the patient presented subacute motor-sensory symptoms involving the upper and lower limbs with mild urinary retention. The neurological examination showed lateral gaze-evoked nystagmus, reduced vibratory sensation hypoaesthesia to the upper and lower limbs (upper level C5) and hyposthenia (4/5 MRC scale) to the left limbs and to the right leg (EDSS 4.0).⁷

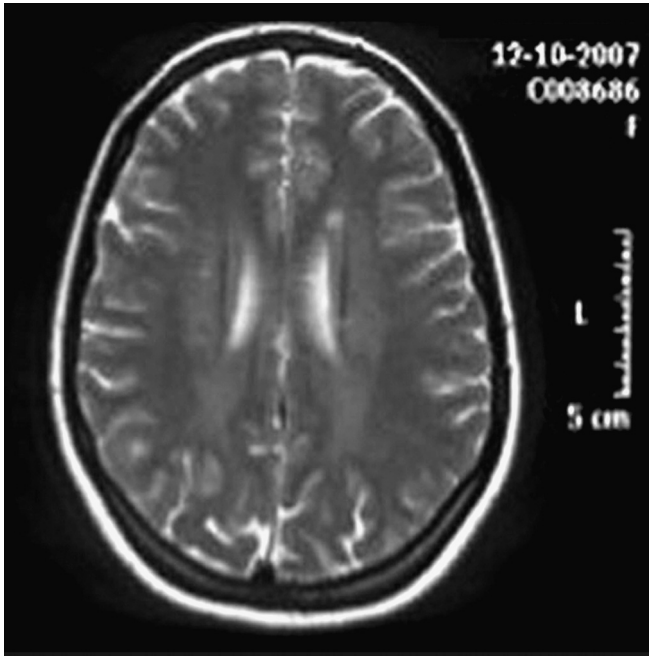


Figure 1.—Axial brain T2-MRI showing periventricular hyperintense lesions coupled with a moderate diffuse white matter hyperintensity.

A cranial and cervical magnetic resonance imaging study revealed periventricular and cervical (C2-C3) T2-hyperintense lesions (Figure 1).

Echo-color Doppler (ECD) screening revealed three positive parameters of anomalous venous return fulfilling the criteria for suspect CCSVI, which was taken as an indication to continue the study using selective venography.^{5, 6}

Selective venography confirmed that anomalies in the ECD venous haemodynamics were due to pronounced extracranial venous stenosis, localized exactly at the distal segment of the left internal jugular vein and at the outlet of the azygous vein into the superior vena cava, configuring a type A pattern of CCSVI (Figure 2, left).

Treatment of the identified venous obstructive lesion at the time of the diagnostic evaluation was performed by means of PTA (Figure 2, right). The procedure was approved by the ethical committee on February 2007; postoperative venograms demonstrated a successful dilatation and the in-patient post-procedural observation lasted 4 hours.

Clinical, neurophysiological, and vascular outcome

Clinical evaluation and EDSS score were assessed by a single neurologist blind to the neurophysiological results.

Method of transcranial magnetic stimulation

A Micromed apparatus was used for motor evoked potential (MEP) recorded from the abductor pollicis brevis and anterior tibial muscles of both sides, using sur-

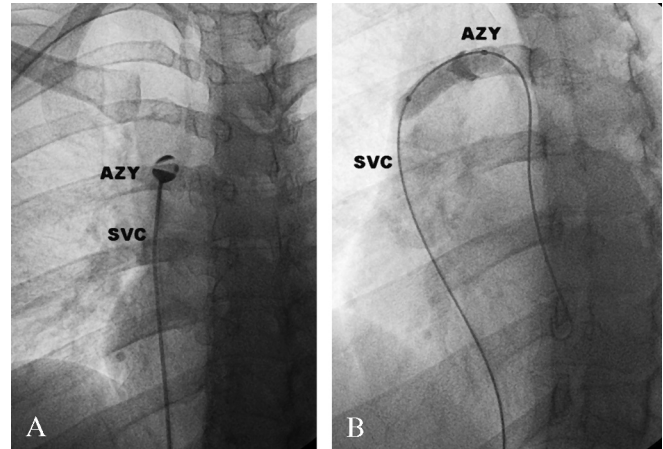


Figure 2.—A) Membranous obstruction of the outlet of the azygous vein (AZY) into the superior vena cava (SVC). The triple septa determines a reflux along the AZY with impaired drainage of the central nervous system. B) Percutaneous transluminal angioplasty performed at the level of the membranous stenosis. The same procedure was performed in the same patient at the point of stenosis of the left internal jugular vein.

face electrodes in a belly-tendon montage. Bandpass filters were 30-3000 Hz.

For TMS we used a Magstim 200 monophasic stimulator with a 9 cm diameter circular coil (Magstim Co, Whitland, Dyfed, UK). The coil was placed over the vertex for the lower limb and 2-3 cm anterior to C3 or C4 for the upper limb, while small movements were made in order to find the largest response. The resting motor threshold (RMT) was measured, defined as the lowest power level (as a percentage of the maximal stimulator output) at which a 50 uV response can be evoked in 50% of ten trials measured at rest.

For every muscle 10 successive stimuli were delivered at an intensity of RMT plus 20% of the maximum stimulator output during a slight voluntary muscle contraction. The MEP latency, defined as the shortest latency in 10 trials, was calculated from the onset of the first negative deflection. The MEP amplitude, obtained from averaging the three largest amplitude responses, and Compound Muscle Action Potential (CMAP) amplitude, recorded by supramaximal electrical stimulation of the median or peroneal nerve, were used to calculate the percentage of the MEP/CMAP ratio.

The F wave shortest latency recorded by supramaximal electrical stimulation of the median or peroneal nerve was used to calculate the Central Motor Conduction Time using the formula:

$$\text{CMCT} = \text{MEP latency} - \frac{[(\text{F wave latency} + \text{CMAP latency} - 1)]}{2} \cdot 8$$

At each evaluation the MEP amplitude, MEP/CMAP ratio and CMCT were analysed.

Baseline data (T0, before treatment) were compared

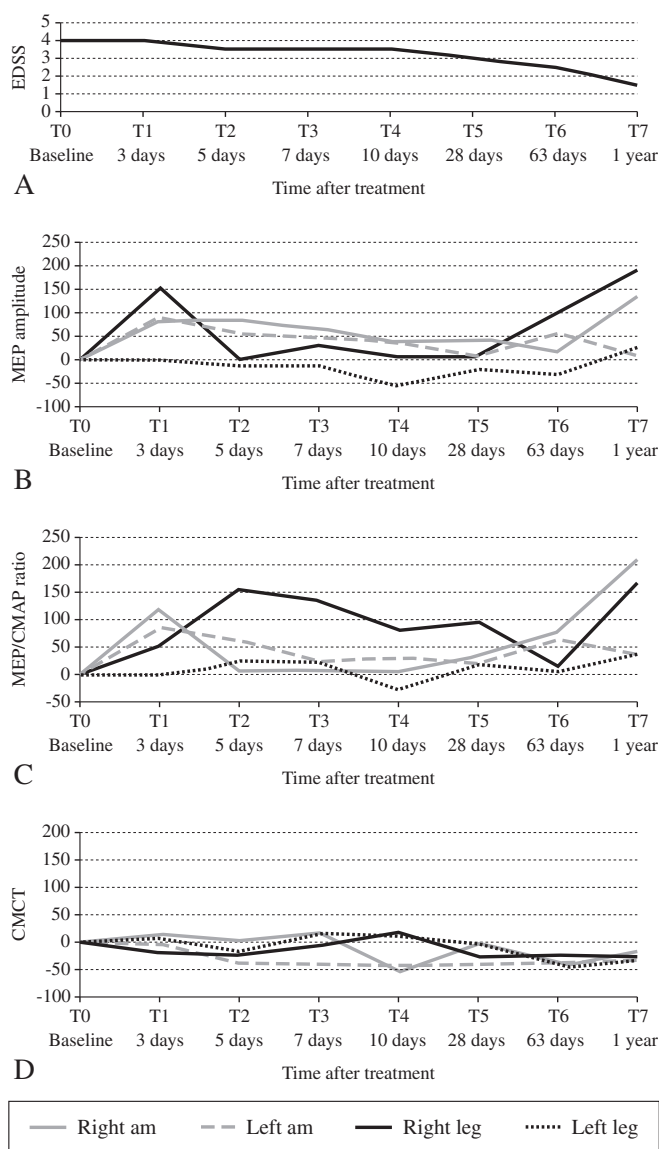


Figure 3.—Changes of EDSS score (A), MEP amplitudes (B), MEP/CMAP amplitude ratio (C) and CMCT (D) at each evaluation, before and after PTA.

Values of each parameter are expressed as a percentage variation from baseline.

- T0 (baseline) – EDSS 4.
- Upper limbs: reduced MEP amplitude and ratio with increased CMCT.
- Lower limbs: MEP amplitude and ratio slightly reduced, CMCT within normal range.
- T1 (3 days after PTA) – EDSS 4.
- Upper limbs: MEP amplitudes and ratio increased, CMCT within the norm.
- Lower limbs: MEP amplitude and ratio increased with reduced CMCT at right leg; no changes at left leg.
- T2 (5 days after PTA) – EDSS 3.5: improvement of sensory deficits.
- Upper limbs: at right arm, reduced MEP amplitude and ratio with no changes in CMCT; at left arm CMCT is within normal range.
- Lower limbs: MEP/cMAP ratio and CMCT improvement at right leg and, to a lesser extent, at left leg.
- T3 (7 days after PTA) – EDSS 3.5: no substantial clinical or neurophysiological changes.
- T4 (10 days after PTA) – EDSS 3.5: no substantial clinical or neurophysiological changes.
- T5 (28 days after PTA) – EDSS 3: clear improvement of the sensory deficits, initial improvement of strength.
- Upper limbs: no changes.
- Lower limbs: further reduction in CMCT.
- T6 (63 days after PTA) – EDSS 2.5: further improvement of the whole motor-sensory picture.
- Upper limbs: MEP amplitudes and ratio increased. Motor evoked potentials are within normal range.
- Lower limbs: normalization of CMCT. Motor evoked potentials are within normal range.
- T7 (one year after PTA) – EDSS 1.5.
- Upper limbs: MEP amplitudes and ratio increased.
- Lower limbs: MEP amplitudes and ratio increased.

to normative data from our laboratory. The values of each parameter at each postoperative observation were expressed as a percentage variation from baseline.

Postoperative ECD demonstrated that the haemodynamic parameters of CCSVI were effectively corrected during follow-up (controls on a three monthly basis).

The trend of the EDSS score and of the MEP amplitudes, MEP/CMAP ratio and CMCT on four limbs at each evaluation are summarised in Figure 3.

At the baseline (T0) there was an evident reduction in the amplitude of MEPs and ratio with increased CMCT in the upper limbs, and slight reduction in the amplitude of MEPs and ratio with normal CMCT in the lower limbs.

After PTA, the course of the amplitude-ratio and CMCT parameters modified in a converse manner: the MEP amplitude and the MEP/CMAP ratio tended to increase, while the CMCT tended to decrease in both upper and lower limbs.

In particular, at T1 the amplitudes and ratio of the upper limbs and of the right lower limb had increased, while the CMCT was within the norm in the upper limbs and further reduced in the right lower limb.

The neurophysiological changes were followed by clinical improvement to sensory deficits at T2. At T6 the patient showed a further clear improvement in the whole motor-sensory picture (EDSS: 2.5). A further increase in the amplitude and the ratio of MEPs in the upper limbs and a normalization of CMCT in all four limbs was recorded: the MEPs are now within the norm.

One year after PTA (T7) the patient was asymptomatic. She presented a slight reduction of vibratory sensation in the lower limbs and brisk reflexes in the left limbs (EDSS: 1.5).

The TMS showed a further increase in MEP amplitudes and ratio in all four limbs, while the CMCT was unchanged.

Discussion and conclusions

TMS monitoring of the outcome of PTA for extracranial venous obstruction associated with MS demonstrated a dramatic improvement in the MAP/CMAP ratio and CMCT, starting from three days after the procedure and persisting over time. The change in neurophysiological data was in turn precocious and was followed by a significant clinical improvement, with a shift on the EDSS scale from a value of 4 to 1.5. The very short time lag between surgical treatment and clinical/neurophysiological improvement is best explained as an effect of the vascular treatment.

Reduction in the CMCT has been described after corticosteroid treatment, but it does not correlate with clinical improvement of the motor deficit because the latter depends only marginally on variations in motor conduction.⁴

In fact, the motor function correlates with the number of conducting central motor neurons: hence, in theory, the amplitude and area of the MEP should reflect motor function better.

In practice, though, these two parameters are not sufficiently sensitive to quantify the motor pathway deficit for various reasons:

- 1) desynchronization of the response due to myelinic damage, which causes phase cancellation leading to a reduction in the MEP amplitude;
- 2) the presence of repeated discharges by the spinal neurons in response to TMS.⁹

An increased number of conducting central motor neurons may explain the modifications to the amplitudes and ratio detected after pharmacological treatment with corticosteroids, but not the modifications to the CMCT.

To explain the increased number of excitable motor neurons, we can hypothesize either a reduction in the conduction blockage or an increase in cortical excitability.¹⁰

We observed an increase in the amplitude and the MEP/CMAP ratio, together with a reduction in CMCT: these findings hardly ever happen at the same time after pharmacological treatment, and lead us to hypothesize a reduction in central motor pathway inhibition secondary either to a reduction of the conduction blockage or to modified excitability of the grey matter.

Moreover, to our knowledge, normalization of the MEP never occurs after corticosteroid treatment or spontaneous resolution of a poussée. Even in patients with MS who present a full clinical recovery after motor involvement, the neurophysiological data always point to a certain degree of sub-clinical impairment.

In our patient the dramatic clinical improve-

ment followed the neurophysiological changes and allowed us to avoid steroid treatment.

The main question is, of course, the relationship between the coherent clinical and neurophysiological course described here, on the one hand, and the haemodynamic correction of the associated CCSVI, on the other. Unfortunately we lack knowledge of how the cerebrovenous system affects the different physiological parameters of normal brain function. However, the relationship between the location of extracranial venous outflow obstructions and the clinical course of MS⁵ as well as the data recorded in the present clinical case suggest that the impact may be greater than previously assumed, and warrants further studies.

The same applies to evaluating how changes in motor pathway excitability and cortical plasticity phenomena are involved in the neurophysiological behaviour of MS patients.

References

1. Benecke R, Meyer BU. Magnetic stimulation of corticoculcular systems and of cranial nerves in man: physiological basis and clinical application. *Electroenceph Clin Neurophysiol Suppl* 1991;43:333-43.
2. Fuhr P, Borggrefe-Chappuis A, Schindler C, Schindler C, Kappos L. Visual and motor evoked potentials in the course of multiple sclerosis. *Brain* 2001;124:2162-8.
3. Fuhr P, Kappos L. Evoked potentials for evaluation of multiple sclerosis. *Clin Neurophysiol* 2001;112:2185-9.
4. Humm AM, Z'Graggen WJ, Bühler R, Magistris MR, Rösler KM. Quantification of central motor conduction deficits in multiple sclerosis patients before and after treatment of acute exacerbation by methylprednisolone. *J Neurol Neurosurg Psychiatry* 2006;77:345-50.
5. Zamboni P, Galeotti R, Menegatti E, Malagoni AM, Tacconi G, Dall'Ara S et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2009;80:392-9.
6. Zamboni P, Menegatti E, Galeotti R, Malagoni AM, Tacconi G, Dall'Ara S et al. The value of cerebral Doppler venous haemodynamics in the assessment of multiple sclerosis. *J Neurol Sci* 2009;282:21-7.
7. Kurtzke J. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;33:1444-52.
8. Rossini PM, Marciani MG, Caramia M, Roma V, Zarola F. Nervous propagation along 'central' motor pathways in intact man: characteristics of motor responses to 'bifocal' and 'unifocal' spine and scalp non-invasive stimulation. *Electroenceph Clin Neurophysiol* 1985;61:272-86.
9. Magistris MR, Rosler KM, Truffert A, Landis T, Hess CW. A clinical study of motor evoked potentials using a triple stimulation technique. *Brain* 1999;122:265-79.
10. Fierro B, Salemi G, Brighina F, Buffa D, Conte S, La Bua V et al. A transcranial magnetic stimulation study evaluating methylprednisolone treatment in multiple sclerosis. *Acta Neurol Scand* 2002;105:152-7.

Corresponding author: R. Plasmati, Department of Neurology, Unit of Neurology, Bellaria Hospital, Via Altura 3, 40139, Bologna, Italy. E-mail: rosaria.plasmati@ausl.bo.it