Is chronic fatigue the symptom of venous insufficiency associated with multiple sclerosis? A longitudinal pilot study

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Aim. **Chronic fatigue (CF) severely affects patients with multiple sclerosis (MS), but its pathogenesis remains elusive and the effectiveness of available treatments is modest. We aimed to evaluate the effect on CF of the balloon dilatation of stenosing lesions affecting the main extracranial veins configuring the chronic cerebrospinal venous insufficiency (CCSVI), a condition strongly associated with MS.**
Methods. **Thirty-one MS consecutive patients (16 males, age 46.2±9.4 years) with associated CCSVI and CF underwent the endovascular procedure. Fatigue was assessed using the Fatigue Severity Scale (FSS) and Modified Fatigue Impact Scale (MFIS) at baseline (T0) and one (T1), six (T6) and twelve (T12) months after the procedure. In ambulatory patients (N.=28), mobility was evaluated using the 6-min walking test at T0 and T1.**
Results. **FSS and MFIS scores significantly improved from preoperative values, and the positive trend was maintained at one year (FSS: T0=5.1±1.0 to T12=3.5±1.8, P<0.001; MFIS-total score: T0=34.9±14.8 to T12=22.5±13.7, P<0.001; MFIS-Physical subscale: T0=21.2±8.0 to T12=13.5±9.7 P<0.001; MFIS-Cognitive subscale: T0=9.2±9.5 to T12=6.0±6.3, P=0.03; MFIS-Psychosocial subscale: T0=4.5±2.1 to T12=2.5±2.1, P<0.001). Six-min walking distance (6MWD) at T1 improved significantly (332±190m to 378±200m, P=0.0002). In addition, an inverted correlation between 6MWD and MFIS-physical subscale variations was found in the subgroup of patients (N.=8) with no lower limb motor impairment (r=-0.74, P=0.035).**
Conclusion. **The reestablishment of cerebral venous return dramatically reduced CF perception in a group of MS patients with associated CCSVI, suggesting that CF is likely the symptom of CCSVI.**
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Key words: **Angioplasty, balloon - Fatigue - Multiple sclerosis - Cerebrovascular accidents - Venous insufficiency.**

Chronic fatigue (CF) is one of the most common symptom affecting people with multiple sclerosis (MS). It is clearly different from normal fatigue and defined as a subjective lack of physical and/or mental energy,[1] or as a state of exhaustion distinct from depressed mood or physical weakness.[2] Up to 86% of patients experience fatigue, and in 30% it's the worst and most disabling symptom.[3-5] It can interfere with the ability to perform daily activities and severely affects quality of life.[6, 7] The association between CF and degree of neurological impairment, physical disability or mood has been variously studied but conclusions are conflicting.[3, 4, 8-13] Despite widely investigated pathogenesis of fatigue, it remains poorly understood.[10, 14] This is reflected in the lack of definite benefits derived from the pharmacologic or non-pharmacologic treatments that are currently available.[14-17]

Recently, a condition defined as chronic cerebrospinal venous insufficiency (CCSVI) has been found to be strongly associated with MS.[18] CCSVI is characterized by multiple stenosing lesions that affect the main extracranial cerebrospinal venous routes, as demonstrated by selective venography (Figure 1). Proximal venous strictures cause abnormal venous haemodynamic with opening of collateral pathways and with a very high incidence of reflux in both intracranial and extracranial venous segments, and loss of the postural regulation of cerebral venous outflow.[18, 19] In an open label prospective study, the safety of balloon dilatation (Percutaneous Transluminal Angioplasty, PTA) of CCSVI stenosing lesions [20, 21] has been demonstrated. We hypothesised that fatigue in MS could be related to the

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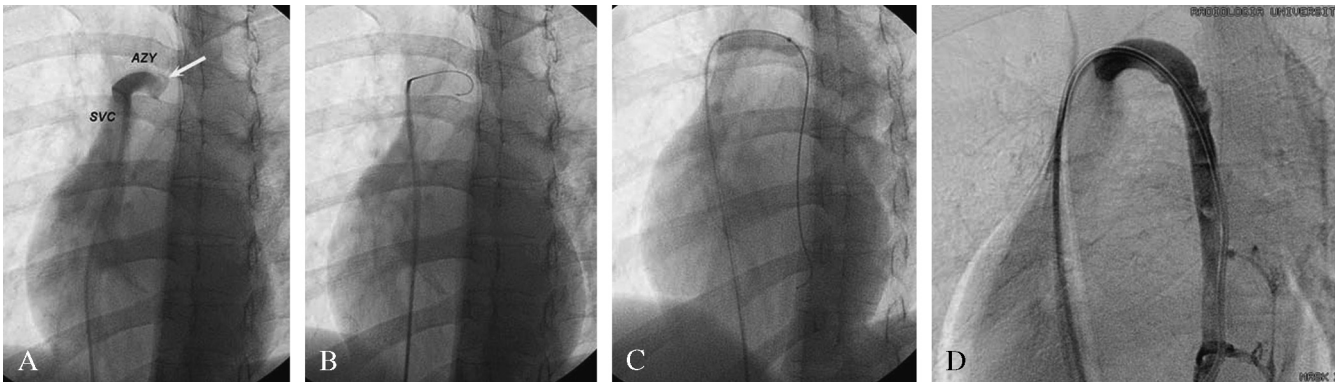

Figure 1.—A) Selective venography demonstrates the membranous obstruction of the azygous vein (AZY) at the level of the arch in a multiple sclerosis patient with chronic fatigue. SVC=superior vena cava. B) The wire cannot pierce the membrane. C) After perforation the balloon is inflated for percutaneous transluminal angioplasty. D) Postoperative control demonstrates the patency of the AZY.

underlying CCSVI, and measured its variation after PTA of extracranial venous stenosis.

Materials and methods

Thirty-five consecutive patients (18 males, age 44.9±10.8 years) with clinically definite MS according to recommended criteria [22] who reported CF were recruited into the study. All patients gave informed consent. The study was approved by the Ethical Committee of Ferrara Hospital.

Patient inclusion criteria were: age 18-65 years; diagnosis of CCSVI pointed out by ≥2 transcranial and extracranial Echo-Color-Doppler-high resolution (TCCS-ECD) criteria;[18, 19] fatigue symptoms present >6months; a mean score of the Fatigue Severity Scale (FSS)[23] >4; and normal renal function.

Exclusion criteria included: relapse or disease progression in the previous three months; the presence of depression or other major diseases; and the intake of medications affecting fatigue in the past three months (for example corticosteroids, antidepressants, amantadine, or modafinil).

Patients were allowed to continue their disease-modifying therapies for MS for the duration of the study.

Study of cerebrospinal venous return

A study of the cerebrospinal venous return was carried out as screening test by means of a TCCS-ECD examination on the basis of the previously described protocol.[18, 19] The diagnosis of CCSVI was performed when at least 2 out of 5 established anomalous haemodynamic criteria were detected:[18, 19]

1) reflux in the internal jugular veins (IJVs) and/or vertebral veins (VVs) with the head in any position;

2) reflux in the deep cerebral veins (DCVs);

3) high resolution B-mode evidence of IJV stenoses;

4) flow not Doppler-detectable in the IJVs and/or VVs;

5) reverted postural control of the main cerebral venous outflow pathways.

Cerebrospinal venous return was monitored in the follow-up at 1 (T1), 6 (T6) and 12 (T12) months after the endovascular procedure.

To define a CCSVI severity level, a TCCS-ECD score ranging from 0 to 16 (lower scores indicate less severity level), named venous haemodynamic insufficiency severity score (VHISS), was calculated as previously described.[24]

Selective phlebography and endovascular procedure

Patients underwent a selective phlebography of the lumbar veins, left renal vein, azygous vein (AZY), and IJVs via catheterization of the left iliac femoral venous axis to confirm the previous TCCS-ECD diagnosis of CCSVI. This procedure also allowed, for the treatment of the identified venous obstructive lesion by means of PTA [20, 21] (Figure 1).

Fatigue assessment

Fatigue was evaluated at baseline (T0), on the day preceding the endovascular procedure, and at T1, T6 and T12 after the endovascular proce-

dure by a trained interviewer (AMM), who was not involved in the neurological or surgical assessment and blinded with respect to patients' vascular outcome. Either the patients or the assessor of fatigue did not know the results of CCSVI monitored by means of postoperative TCCS-ECD. At each study visit, questionnaires were administrated by the same interviewer at the same hour of the day and in the same outpatient clinic.

To provide a more complete evaluation, fatigue was assessed using two scales, the Fatigue Severity Scale (FSS) [23] and the Modified Fatigue Impact Scale (MFIS).[1]

FSS is the most used scale to quantify severity of fatigue in MS. It has been shown to have a high degree of internal consistency, validity, and sensitivity to changes in clinical condition.[23] It consists of 9 questions mainly focus on physical symptoms with an average score ranging from 1 to 7 (lower scores indicate less fatigue).

MFIS, the most recent and shortened version of the Fatigue Impact Scale,[4] is the instrument recommended by the fatigue guidelines development panel of the MS Council for Clinical Practice Guidelines.[1] It comprises 21 items divided into 3 subscales: physical (9 items), cognitive (10 items) and psychosocial (2 items) functioning. Each item has a score ranging from 0 to 4 with a total score from 0 to 84 (lower scores indicate less fatigue).

Mobility assessment

All ambulatory patients (N.=28) underwent a 6-min walking test [25, 26] at T0 and at T1. Patients were instructed to walk up and down a 22 m corridor at their own pace for 6 minutes aiming to cover as much distance as possible. The distance completed after 6 minutes (6MWD) was recorded. At each study visit test was performed in the same temperature-controlled setting maintaining constant for each patient the hour of execution. Patients with gait impairment who needed an assistive device were asked to use their customary device, which was used for all subsequent assessments.

Statistical analysis

Data are expressed as mean±SD. The normal distribution of data was verified by the Kolmogorov-Smirnov test. The agreement between the FSS score and the MFIS total score for each follow-up interval was assessed using Pearson's correlation coefficient and Passing Bablock regression analysis. Differences of FSS score and MFIS score between baseline and follow-up were tested for significance with one-way analysis of variance (ANOVA), and the Student-Newman-Keuls test was used for all pairwise comparisons. Differences in fatigue scores among MS clinical types were assessed with repeated measures ANOVA. A Pearson correlation was conducted to evaluate the relationship between baseline fatigue scores and their variations during follow-up (values at T1, T6, T12 minus value at T0), and VHISS and number of lesions for each patient. Finally, a paired Student t-test was used to compare the 6MWD at T0 and T1, and a regression analysis was performed to assess the relationship between 6MWD and MFIS-Physical subscale score variations (values at T1 minus values at T0). Data were analysed using the software program MedCalc 10.0 (MedCalc Software, Mariakerke, Belgium).

Results

Four out of thirty-five patients were excluded for FSS scores <4. Thirty-one patients (16 males, age 46.2±9.4 years) were finally enrolled in the study. MS type, according to established criteria,[27] included in our study population were: relapsing-remitting (RR) 42% (N.=13), secondary progressive (SP) 26% (N.=8), primary progressive (PP) 32% (N.=10).

Demographics and clinical characteristics of the study population are reported in Table I.

TABLE I.—*Clinical and demographic characteristics of the study population.*

	Patients (N.=31)
Age, years	46.2±9.4
Male, % (male/female)	52% (16/15)
MS clinical course, N. (% of patients)	
Relapsing-remitting	13 (42%)
Primary progressive	8 (26%)
Secondary progressive	10 (32%)
Disease duration, years	10.8±7.1
EDSS	3.8±2.2

Data are expressed as mean±SD. EDSS: Expanded Disability Status Scale.

TABLE II.—*Values of FSS and MFIS scores of the study population (n=31) at baseline (T0), 1 month (T1), 6 months (T6), and 12 months (T12) after the endovascular treatment.*

	T0	T1	T6	T12	P
FSS	5.1±1.0	3.2±1.5*	3.2±1.8*	3.5±1.8*	<0.001
MFIS	34.9±14.8	15.9±13.4*	20.3±14.9*	22.5±13.7*	<0.001
pMFIS	21.2±8.0	10.5±7.8*	13.3 ±9.7*	13.5±9.7*	<0.001
cMFIS	9.2±9.5	3.7±6.4*	5.1±6.4	6.0±6.3	=0.03
psMFIS	4.5±2.1	1.8±1.9*	1.9±2.1*	2.5 ±2.1*	<0.001

Data are expressed as mean±SD. FSS: Fatigue Severity Scale; MFIS: Modified Fatigue Impact Scale total score; p, physical, c, cognitive and ps, psychological MFIS subscales. P value, one way ANOVA. *A significant decrease in the perception of fatigue in all follow-up intervals as compared with baseline values. No differences among the times of follow-up.

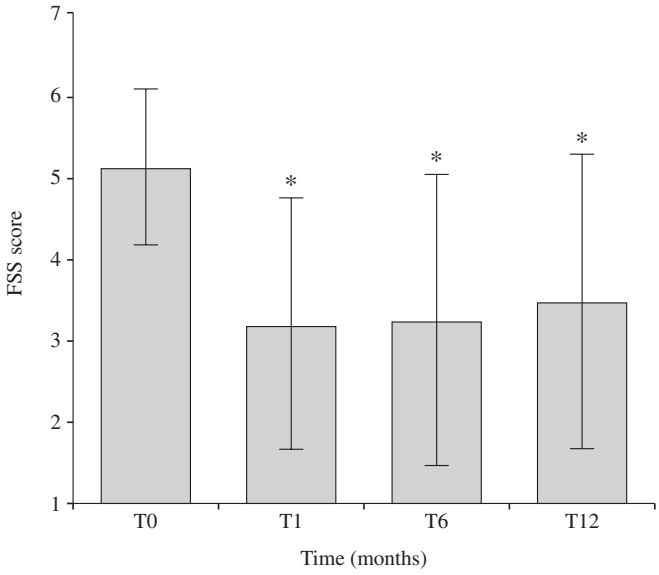

Figure 2.—Mean scores±SD of the Fatigue Severity Scale (FSS) at baseline (T0) and one month (T1), 6 months (T6), 12 months (T12) after the endovascular treatment. *A significant decrease in the perception of fatigue in all follow-up intervals as compared with baseline values (one-way ANOVA P<0.001). No differences among the times of follow-up.

Study of cerebrospinal venous return

At least two out of five criteria required for establishing the non-invasive diagnosis of CCSVI by means TCCS-ECD examination were detected in all study patients.

The mean value and SD of VHISS was 9.9±2.4.

During the postoperative monitoring of patients, at T1, T6 and T12, despite the mean number of TCCS-ECD criteria of CCSVI was <2, restenosis in one IJV occurred in 3 patients (RR, N.=2, SP, N.=1) at T6 and in 4 patients (RR, N.=1, SP, N.=1, PP, N.=2) at T12, and were documented by reflux or blocked flow reappearance. The 3 RR patients who presented the restenosis, also experienced a clinical relapse. No patients presented increased postoperative Expanded Disability Status Scale during follow-up.

Selective phlebography and endovascular procedure

A multiple significant extracranial venous stenosis were found in all the study patients so confirming the diagnosis of CCSVI performed by means of TCCS-ECD examination. Consequently PTA was performed in the AZY in 28/31 (90%) patients, in the left IJV in 24/31 (77%) patients and in the right IJV in 24/31 (77%) patients. Mean number and SD of lesions for each patients was 3±1. All procedures were performed in day hospital under local anesthesia and well tolerated. Post-procedural observation was carried out at 4 hours and the patients were discharged with a compressive dressing in the left groin, the preferred site of vascular access. The dressing could be removed the day after the procedure. A prophylactic dose of low-molecular-weight heparin was administered for the subsequent 3 weeks.[28] No operative and postoperative complications, including vessel rupture, thrombosis, or side effects caused by the contrast media, were registered. Minor haemorrhages with haematomas in the site of vascular access were occasionally seen.[20, 21]

Fatigue assessment

All patients completed the study at T1 and T6. At T12, five patients dropped out owing to personal reasons (N.=2), the intake of medications that potentially affected fatigue (N.=1), or femoral fracture or other trauma (N.=2).

The FSS score and the MFIS total score for each follow-up period were significantly correlated (T0: r=0.54, P<0.001; T1: r=0.66 P=0.0001; T6: r=0.80.

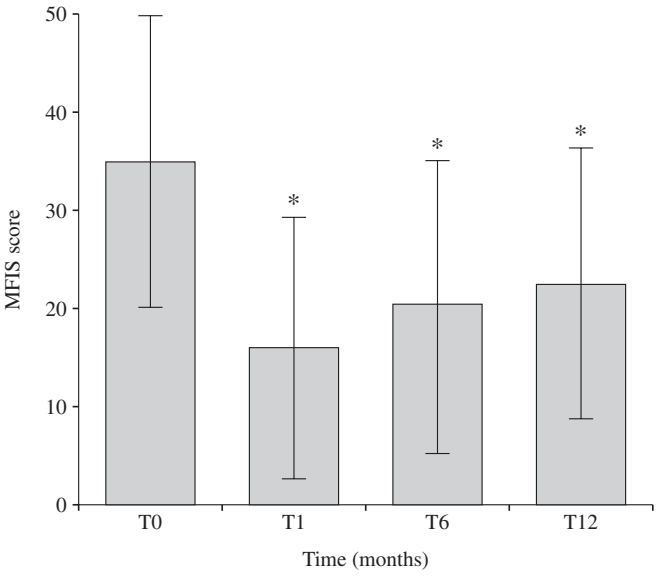

Figure 3.—Mean scores±SD of the Modified Fatigue Impact Scale (MFIS) at baseline (T0) and one month (T1), 6 months (T6), 12 months (T12) after the endovascular treatment. *A significant decrease in the perception of fatigue in all follow-up intervals as compared with baseline values (one-way ANOVA P<0.001). No differences among the times of follow-up.

P<0.0001; T12: r=0.82, P<0.0001) and were in good agreement (Passing-Bablock analysis: no significant deviation from linearity, P>0.10).

Compared with the baseline value, the FSS score decreased significantly and remained stable over time (P<0.001), as shown in Table II and Figure 2. Analogous results were obtained for the MFIS total score (Table II, Figure 3) and for the Physical and Psychosocial subscale scores (Table II). Cognitive subscale scores showed an improvement over time but were significantly different only at T1 (P=0.03) (Table II). Among MS clinical types no significant differences were found in the FSS score and MFIS scores over time except for Psychosocial subscale (P=0.01) (Table III). No relationship were found between baseline FSS score, MFIS scores and their variations during follow-up, and VHISS and number of lesions for each patient.

Mobility assessment

In the group of patients assessed for mobility (N.=28), 6MWD at T1 improved significantly compared with baseline values (332±190 m to 378±200 m P=0.0002). In addition, an inverted relationship (r=-0.74, P=0.035) between 6MWD and MFIS-physical subscale score variations was found in the subgroup of patients with no lower limb motor impairment (N.=8), whereas no correlation was found in the entire cohort.

TABLE III.—*Values of FSS and MFIS scores of the study population divided for MS clinical type at baseline (T0), 1 month (T1), 6 months (T6), and 12 months (T12) after the endovascular treatment.*

		Relapsing remitting (N.=13)	Primary progressive (N.=10)	Secondary progressive (N.=8)
FSS	T0	4.8±0.8	5.3±1.1	5.4±1.0
	T1	2.3±1.1	4.0±1.7	3.6±1.3
	T6	2.5±1.5	3.8±2.0	3.8±1.9
	T12	2.4±1.3	4.1±2.2	4.0±1.6
MFIS	T0	33.6±19.2	32.9±12.9	39.3±7.3
	T1	12.6±13.1	14.5±12.6	23.1±13.7
	T6	16.7±14.3	21.2±15.5	24.8±15.3
	T12	15.1±9.6	25.3±17.0	30.8±11.5
pMFIS	T0	18.2±8.7	22.4±7.8	24.5±5.9
	T1	7.7±6.7	10.1±6.6	15.4±9.5
	T6	9.7±7.4	15.3±11.1	16.8±10.2
	T12	7.3±6.0	16.4±11.1	20.3±9.1
cMFIS	T0	12.2±10.5	5.4±8.4	9.0±8.3
	T1	3.8±5.6	3.0±7.8	4.4±6.6
	T6	6.0±6.7	3.7±6.6	5.4±6.3
	T12	5.4±5.3	5.0±7.3	7.2±6.6
psMFIS	T0	3.2±2.1	5.1±1.9	5.9±1.2
	T1	1.2±1.8	1.4±1.1	3.4±2.0
	T6	1.0±1.6	2.2±2.0	2.3±2.6
	T12	1.0±1.0	4.0±1.9	3.3±2.3

Data are expressed as mean±SD. FSS: Fatigue Severity Scale; MFIS: Modified Fatigue Impact Scale total score; p, physical, c, cognitive and ps, psychological MFIS subscales. Statistical analysis: repeated measures analysis of variance, no differences between groups except for psMFIS scale (P=0.01).

Discussion

Fatigue in MS has been widely investigated, but its pathogenesis remains still elusive.[10, 14] Therefore, an effective treatment has not yet been found.[14-17] Fatigue is a multidimensional symptom, and many factors, that some authors have classified as modifiable and not modifiable,[29] can be involved in its clinical manifestation. We hypothesised that CF in MS could be related to the underlying CCSVI, and measured its variation after PTA of extracranial venous stenosis. The main finding of the present pilot study was that the reestablishment of a normal cerebrospinal haemodynamic condition dramatically reduced the perception of fatigue in a group of MS patients. Furthermore, the reduction in fatigue was maintained over time even though with a decreasing trend. There are two possible explanations of the relative decline over time of the fatigue scores (Table II, Figures 2, 3): 1) seven patients showed in the follow-up the occurrence of restenosis in one IJV, respectively 4 at T6 and 3 at T12. We hypothesise that restenosis may cause increased fatigue perception; 2) in the first month of follow up a quote of placebo effect might be responsible of the reduced fatigue perception likely reducing its impact along time.

All patients, even those who perceived moderate fatigue at baseline evaluation, reported a much greater ability to perform their daily activities and a new dynamic condition absolutely different from that one they were used to. It could be argued that the perception of decreased fatigue is only a placebo effect. For this reason, we also measured the mobility before and one month after the endovascular procedure, demonstrating improvement without any specific conditioning under objective conditions. Therefore, in the subset of patients with no motor impairment and normal walking ability in which fatigue is more likely to be the activity-limiting factor, we found a strong relationship between reduction in the perception of fatigue and improved patient performance. This provides clear and objective evidence that PTA can be an effective treatment for fatigue. This is particularly relevant because of the safety of PTA [20, 21] and the lack of effective pharmacologic and non-pharmacologic treatments for fatigue.[14-17]

One previous study showed a strong association between CCSVI and MS.[18] We believe that these two conditions present interdependent symptoms and possibly interdependent pathophysiologic aspects. However, the results of the present study strongly suggest a direct relationship of CF with CCSVI. In fact the reestablishment of a normal cerebrovenous drainage, proved by the correction of TCCS-ECD parameters of CCSVI, is significantly associated with a dramatic reduction of fatigue perception. Moreover the actual pharmacologic treatment of MS is mainly focused on the autoimmunitary and inflammatory aspects of the disease. Early disease modifying treatments demonstrated to significantly reduce the rate of relapse, the rate of gadolinium enhanced lesions at MRI and ultimately the disability progression, representing a necessary therapeutic measure in these patients.[30, 31] Nevertheless many disabling symptoms such as CF, pain, spasticity, bladder and bowel dysfunctions, sexual dysfunction, are actually orphan of effective treatments.[14-17, 32]

PTA of the IJVs and AZY has been recently demonstrated to be a safe and acceptable treatment with a rate of negligible complications and capable to further positively modify the outcome of associated MS.[20, 21] In the present study it demonstrates an unsuspected effectiveness in improving CF, raising the question if it might be related to the associated condition of CCSVI.

Our study has some limitations typical of a pilot study. The sample is small and also composed of patients who reported a moderate or borderline level of fatigue;[9, 33] both operator and patients were not blinded with respect to the procedure, but only with respect to patients' vascular outcome. The fact that fatigue outcome measures were based on subjective, self-reported instruments, though accepted and validated, could present an additional limitation. In contrast, fatigue is a subjective experience, and self-reporting scales are believed to be appropriate.[5, 14, 34]

Conclusions

In conclusion, our pilot study demonstrated that the reestablishment of a normal cerebrospinal venous return by means of PTA dramatically reduced CF perception in a group of MS patients with associated CCSVI both in acute and in the long-term, suggesting that CF is probably a symptom related to CCSVI.

A further randomised controlled trial in a larger population will enable us to confirm these results and to evaluate the possibility of treating CF in MS by means of adjunctive endovascular treatment. It will also allow us to better understand the complex mechanisms involved in generating this disabling symptom.

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