

# Multiple sclerosis and venous angioplasty for chronic cerebrospinal venous insufficiency: A case control study with ten years follow-up with patients at their own control

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## Abstract

Progressive neurological diseases (PND), such as multiple sclerosis (MS) and chronic cerebrospinal venous insufficiency (CCSVI), have two terms in common, “progressive” and “chronic”, meaning that there is not a definitive therapy at the moment. The aim of our study was to better delineate a link between these two conditions from a cohort of 482 patients diagnosed with relapsing-remitting multiple sclerosis (RRMS) in a 10-years lapse.

The clinical aspects are built on symptoms, upon which the definition of “progression” is based and hence classified. Changes and worsening of symptoms, allow for a classification of the disease and adjustments are effectively an “up-to-date” of the disease itself.

We here resume the 10-years case-control study of 482 MS affected patients with co-existing CCSVI: 314 females, 168 males; mean age = 37.8, classified by their neurology physicians as relapsing-remitting (RR), assessed by the Kurtzke expanded disability status scale (EDSS), and in parallel monitoring changes of the most complained symptoms that were declared by the patients themselves.

Patients were divided in two homogeneous RRMS groups, and then listed in two subgroups as “treated and non-treated for CCSVI” with vein angioplasty (vPTA). Furthermore, a patient’s self-classification, based upon severity and worsening of the symptoms in presence of CCSVI, was developed on the basis of both clinical and Duplex vascular issues and this allowed us to create three severity grade subgroups going from grade 1 to 3, the latter being the most disabling.

Therefore, our results here document the existence of a close parallelism between RRMS-related Duplex imaging and clinical symptoms with CCSVI worsening. Moreover, patients in the group with a less severe condition, grade 1, who underwent vPTA declared significant improvements of their symptoms, encouraging the use of this

procedure as a promising therapeutic approach to slow down disease progression.

## Introduction

The diagnosis of multiple sclerosis (MS) is quite commonly based on the revised McDonald criteria, a combination of clinical findings, imaging, and laboratory data.<sup>1</sup> The diagnosis of MS is defined by the demonstration of the propagation of MS disease characteristics in space and time.<sup>2</sup>

Drug therapy applied to progressive neurological diseases, like MS, so far has not totally stopped the diseases’ progression towards chronicity. There are nine classes of disease-modifying therapies (DMT) available for relapsing-remitting (RR) in MS, with varying mechanisms of action and routes of administration.<sup>2</sup> Nevertheless, if patients have broadened their view towards further horizons and opportunities, this should be understood. The onset of the disease usually occurs in young adults, between their second and third decade, and a lifelong approach to drugs is not always easily accepted.

In literature, diet protocols<sup>3-5</sup> are mentioned for MS patients commonly out of fear of hypersensitive food ingestion, which may suggest to be responsible of the T-cells activation and blood-brain-barrier (BBB) damage according to the Gell and Coombs classification.<sup>6,7</sup>

Furthermore, diet protocols are quite often associated with chelating therapy.<sup>8-10</sup>

Several authors concentrate upon the BBB issues,<sup>11-15</sup> while others have reached negative viewpoints about eventual venous issues, such as chronic cerebrospinal venous insufficiency (CCSVI), denying not only the issue itself but also any possible therapy and consequent results.<sup>16,17</sup> It should here be remembered that carotid endarterectomy, which is now a well-accepted common stroke prevention technique in a subset of patients, was questioned as recently as 1984.<sup>18</sup>

Ever since several authors introduced the issue,<sup>19-25</sup> starting from 2010, we observed abnormal Duplex imaging and clinical CCSVI as a particularly frequent condition in MS. Abnormalities regarded principally internal jugular vein malformations, such as stenosis or hypo-trophic veins, abnormal valve leaflet functions and subsequent blood block or reflux. Similar situations occurred to the medullar venous drainage. Initially, observational reports mainly presented Duplex results matching

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them with the MS disease, regardless of its stage and clinical classification.<sup>26-28</sup> Other non-operator-dependent non-invasive assessment confirmed our Duplex findings, as well as gold standard catheter venography.<sup>29-31</sup>

Here, the highlight is upon a 10-years Duplex survey, combined with patients’ individual observations of their MS disease symptoms, and clinical situations exclusively within the RR population. Quite impressively, the patients elaborated their own classification that we scored and interpreted: a 10-years road-map of their disease.

## Materials and methods

The study is constructed on 482 MS-affected patients (314 females, 168 males; mean age = 37.8), divided in two groups. The first being a population of 264 consecutive MS RR patients (176 females and 88 males with mean age at conclusion of the survey of 38.3 years) who underwent vein angioplasty (vPTA) and were controlled in a lapse of 10 years (November 2010-March 2021). The second being a control group developed from other 218 patients (135 females and 83 males with mean age at con-

clusion of the survey of 37.2 years), with a similar RR-MS pattern. They originally underwent Duplex study for CCSVI between 2010 and 2013 and resulted positive according to the CCSVI classification criteria,<sup>19,20,23</sup> but none proceeded with a vPTA (no-vPTA). This control group grew from people who returned for a new Duplex exam between 2016 and first term of 2021. For all, individual, clinical and symptom evolution of the disease was collected with a personal chart regarding Duplex situation and/or clinical symptoms. (Table 1 is a blank example).

All were classified by their neurology physicians as RR clinical course and assessed for disability in accordance with the Kurtzke expanded disability status scale (EDSS).<sup>32</sup> All of them gave their voluntary participation in the survey, which was in total respect of the Helsinki Ethical Principles,<sup>33</sup> that developed between 2010 and 2021 (10 years). Their monitoring was achieved by means of both Duplex imaging and clinical evaluation. The most frequent symptoms and related side effects, that may affect patients' quality of life (QoL) including family relations and daily work were incorporated: diplopia, fatigue, headache, upper limb numbness and mobility, lower limb numbness and mobility, thermic sensitivity, bladder control, balance coordination, quality of sleep, vertigo, mind concentration and working activity capacity completed the list of symptom issues.

The aim was to complete the natural prosecution of a previous manuscript<sup>28</sup> for the first vPTA group, compared to a control no-vPTA group.

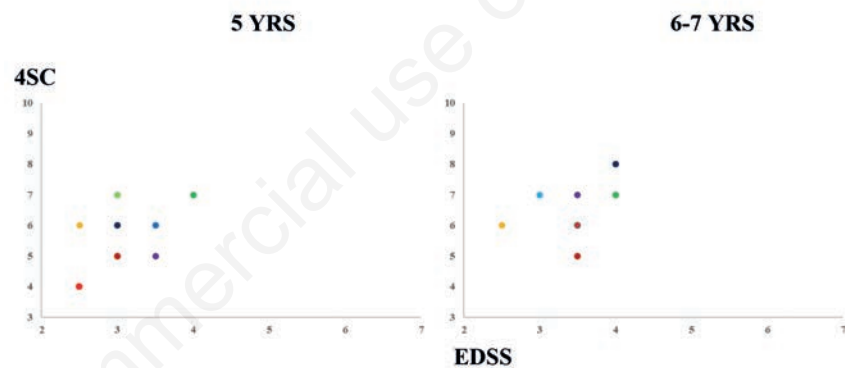
For all 482 patients, QoL evolution in time was subjectively described as "unchanged, moderately or severely worsened" in 10 years.

To assess the presence and the entity of the chronic cerebrospinal venous insufficiency (CCSVI), we performed protocol Duplex imaging,<sup>19,20,23,26,27</sup> that was acquired with high-resolution linear phase probes. The employed machines are here omitted to avoid possible conflicts of interest. All the Duplex exams were carried-out by the same vascular surgeon specialist within constant environmental conditions and comfort for the patients. According with the Duplex imaging protocol, the exams were performed in two different and consecutive positions: first lying-down (00° position) and subsequently sitting-up (90° position). Morphologic abnormalities of the internal jugular veins, in particular diminished calibres, stenosis, abnormal valve leaflets for structure (*i.e.*, an irregular and idle length) and orientation (*i.e.*, against the bloodstream direction) and hypo-motility at pro-

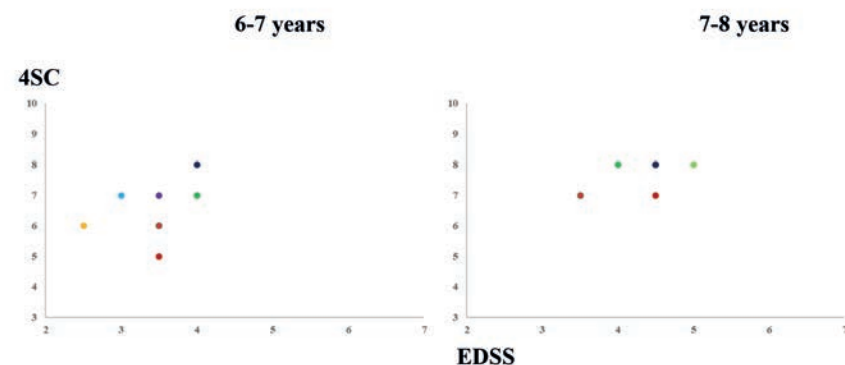
gressive inhale and exhale exercises, were searched along the entire bilateral extra cranial neck district. The blood-flow velocity was evaluated for haemodynamically significant variations, possibly compatible with stenosis or presence of valve abnormalities or abnormal bloodstream reflow. For topographic utility, the internal jugular vein was mapped in sectors going from J0 to J3, the first being at the brachiocephalic junction and the latter just below the vein passage into the skull. A successive evaluation, in this case dynamic, was performed on patients that complained a suspected evolution of their disease towards a secondary progressive (SP) phase. The Duplex was performed by asking the patients to sit in an upright position and inviting them to

gradually assume the so-called "turtle-neck" position. This phase served to determine eventual extrinsic muscle compression on the internal jugular vein, generally being the omohyoid muscle involved.<sup>34,35,37,40</sup> The reason for this manoeuvre was to reproduce the frequent "forwards slanting" position when using a walking-aid device. In our controlled series and accordingly with the results obtained by Zamboni *et al.*,<sup>31</sup> the angioplasty procedures resulted being safe for the patient.

Furthermore, patients individually were asked to quantify their symptoms with a 0-10 mark, as further described as self-symptom severity score classification (4SC), that was subsequently listed in a personal chart, year after year at each follow-up (as shown



**Figure 1.** Vein angioplasty group (9 patients) - grade III. Neurological evaluation Kurtzke expanded disability status scale (EDSS) and self-symptom severity score classification (4SC) change from 5 years to 6-7 years. The change from 5 years to 6-7 years is not significant (with alpha level = 0,05), both for neurological evaluation Kurtzke expanded disability status scale and self-symptom severity score classification.



**Figure 2.** Vein angioplasty group (9 patients) - grade III. Neurological evaluation Kurtzke expanded disability status scale (EDSS) and self-symptom severity score classification (4SC) change from 6-7 years to 7-8 years. Scores for both neurological evaluation Kurtzke expanded disability status scale and self-symptom severity score classification in 7-8 years are significantly different (with alpha level = 0,05) from 6-7 years evaluation.

in Table 1). As a result of this, patients of both groups were included in three lists characterized by low, moderate and high-grade symptoms (severity grade I, grade II and grade III, respectively). To monitor the progression of the disease and the worsening of the symptoms, patients self-attributed a severity score to each symptom, which spread from 1 to 10. This score was re-evaluated at each Duplex control, that commonly occurred each year for the v-PTA treated population (Tables 2A-C).

The self-symptom severity score classification (4SC) figured out individual complexity: grade 1 from 0 to 4 marks, grade 2 from 5 to 6 marks, grade 3 from 7 to 10 marks.

Individually summing the marks of the 12 most usually complained symptoms, the grade I total score section - the less severe - was between 0 and 48 marks meaning a RR situation constant in time, causing affordable issues in everyday life quality (Table 2A).

The grade II total score section - an intermediate condition - was between 49 and 72 marks. This meant an evolutive situation for some symptoms that gradually worsened, and a moderately compromised life quality in presence of some mobility issues that required outdoor aids when moving for longer distances. In the whole the QoL situation was defined as "still acceptable" (Table 2B).

The grade III total score section - the worse and most disabling - over 72 marks, resulted in an actively changing RR or an evolution towards a SP disease with mobility issues that required frequent aids, both in

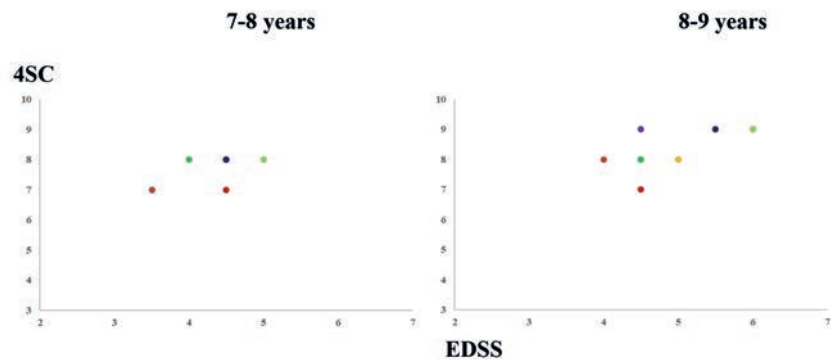


Figure 3. Vein angioplasty group (9 patients) - grade III. Neurological evaluation Kurtzke expanded disability status scale (EDSS) and self-symptom severity score classification (4SC) change from 7-8 years to 8-9 years. Scores for both neurological evaluation Kurtzke expanded disability status scale and self-symptom severity score classification in 8-9 years are significantly different (with alpha level = 0,05) from 7-8 years evaluation.

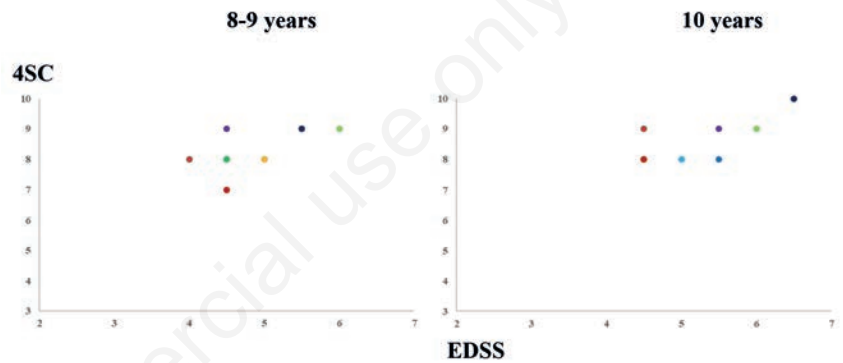


Figure 4. Vein angioplasty group (9 patients) - grade III. Neurological evaluation Kurtzke expanded disability status scale (EDSS) and self-symptom severity score classification (4SC) change from 8-9 years to 10 years (final). The change from 8-9 years to 10 years is not significant (with alpha level = 0,05), both for neurological evaluation Kurtzke expanded disability status scale and self-symptom severity score classification.

Table 1. Example of individual follow-up time table (blank). Symptom classification range: (score from 0 to 10), as given by patients and/or their physician: 0-4 (up to 16 in total) relapsing-remitting described as mild and tolerable 5-6 (up to 63 in total) relapsing-remitting described as an issue that limits quality of life and reduces autonomy 7-10 (up to 105) relapsing-remitting that is evolving or has evolved towards a secondary progressive disease with mobility problems

Patient example: symptoms evolution in 10 years: date, age, gender.

Symptoms	Zero	1Yr	2Yrs	3Yrs	4Yrs	5Yrs	6Yrs	7Yrs	8Yrs	9Yrs	10Yrs	Final Situation	Score
Diplopia	0	0	0	0	0	0	0	0	0	0	0	0	0
Fatigue	0	0	0	0	0	0	0	0	0	0	0	0	0
Headache	0	0	0	0	0	0	0	0	0	0	0	0	0
Upper limb numbness	0	0	0	0	0	0	0	0	0	0	0	0	0
Lower limb numbness	0	0	0	0	0	0	0	0	0	0	0	0	0
Thermic sensibility	0	0	0	0	0	0	0	0	0	0	0	0	0
Bladder control	0	0	0	0	0	0	0	0	0	0	0	0	0
Balance coordination	0	0	0	0	0	0	0	0	0	0	0	0	0
Quality of sleep	0	0	0	0	0	0	0	0	0	0	0	0	0
Vertigo	0	0	0	0	0	0	0	0	0	0	0	0	0
Mind concentration	0	0	0	0	0	0	0	0	0	0	0	0	0
Working activity	0	0	0	0	0	0	0	0	0	0	0	0	0
TOTAL	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 2. A) Score classification (1 to 4) self-evaluated by both vein angioplasty patients (left column) and no vein angioplasty patients (right column) is reported. The number of patients with grade I disability displaying different scores for each symptom is reported (number in bold/score). Their percentage is also reported (in parenthesis). The sum of scores is displayed in line 13. Although still in this grade 1 table, the no vein angioplasty have worst range scores. Relapse-remitting Kurtzke expanded disability status scale is confirmed for all. B) Score classification (5 to 6) self-evaluated by both vein angioplasty patients (left column) and no vein angioplasty patients (right column) is reported. The number of patients with grade II disability displaying different scores for each symptom is reported (number in bold/score). Their percentage is also reported (in parenthesis). The sum of scores is displayed in line 13. Relapse-remitting Kurtzke expanded disability status scale is still confirmed. C) Score classification (7 to 10) self-evaluated by both vein angioplasty patients (left column) and no vein angioplasty patients (right column) is reported. The number of patients with grade III disability displaying different scores for each symptom is reported (number in bold/score). Their percentage is also reported (in parenthesis). The sum of scores is displayed in line 13.

Table 2A		Grade I: 4SC out of 482 patients	
253 vPTA			182 no-vPTA
<b>Patients</b> /scores from 0 to 4 (%)			<b>Patients</b> /scores from 0 to 4 (%)
<b>253/0</b> (100%)	Diplopia		<b>48/1</b> (26.37%); <b>20/2</b> (11.00); <b>68/3</b> (37.36); <b>46/4</b> (25.27)
<b>241/1</b> (95.26%); 12/2 (4.74%)	Fatigue		<b>23/3</b> (12.64); <b>159/4</b> (87.36)
<b>253/0</b> (100%)	Headache		<b>170/2</b> (93.40); <b>12/3</b> (6.60)
<b>240/1</b> (94.86%); 13/2 (5.14%)	Upper limb mobility		<b>116/2</b> (63.74); <b>17/3</b> (9.34); <b>49/4</b> (26.92)
<b>240/1</b> (94.86%); 13/2 (5.14%)	Lower limb mobility		<b>116/2</b> (63.74); <b>17/3</b> (9.34); <b>49/4</b> (26.92)
<b>253/1</b> (100%)	Thermic sensibility		<b>70/2</b> (38.46); <b>15/3</b> (8.24); <b>97/4</b> (53.30)
<b>250/1</b> (98.81%); 3/2 (1.19%)	Bladder control		<b>51/2</b> (28.02); <b>10/3</b> (5.50); <b>121/4</b> (66.48)
<b>249/1</b> (98.41%); 4/2 (1.59%)	Balance coordination		<b>110/2</b> (60.44); <b>72/3</b> (39.56)
<b>253/1</b>	Quality of sleep		<b>69/2</b> (37.91); <b>24/3</b> (13.19); <b>89/4</b> (48.90)
<b>210/0</b> (83%); 43/2 (17%)	Vertigo		<b>170/2</b> (93.40); <b>12/3</b> (6.60)
<b>253/0</b> (100%)	Mind concentration		<b>15/2</b> (8.24); <b>17/3</b> (9.34); <b>150/4</b> (82.42)
<b>210/1</b> (83%); 43/2 (17%)	Work skill		<b>17/2</b> (9.34); <b>89/3</b> (48.90); <b>76/4</b> (41.76)
Score sum between 8 and 16	TOTAL		Score sum between 22 and 41

Table 2B		Grade II intermediate: 4SC out of 482 patients	
vPTA (2 People) (0.75%)			no-vPTA (14 People) (6.42%)
<b>Patients</b> /scores from 5 to 6 (%)			<b>Patients</b> /scores from 5 to 6 (%)
<b>2/5</b> (100%)	Diplopia		<b>10/5</b> (71.43%); <b>4/6</b> (28.57%)
<b>1/5</b> (50%); 1/6 (50%)	Fatigue		<b>7/5</b> (50%); <b>7/6</b> (50%)
<b>2/4</b> (100%)	Headache		<b>11/5</b> (78.57%); <b>3/6</b> (21.43%)
<b>2/6</b> (100%)	Upper limb mobility		<b>12/5</b> (85.71%); <b>2/6</b> (14.29%)
<b>2/6</b> (100%)	Lower limb mobility		<b>12/5</b> (85.71%); <b>2/6</b> (14.29%)
<b>2/4</b> (100%)	Thermic sensibility		<b>13/5</b> (92.86%); <b>1/6</b> (7.14%)
<b>1/5</b> (50%); 1/6 (50%)	Bladder control		<b>10/5</b> (71.43%); <b>4/6</b> (28.57%)
<b>2/5</b> (100%)	Balance coordination		<b>14/5</b> (100%)
<b>2/5</b> (100%)	Quality of sleep		<b>14/4</b> (100%)
<b>1/5</b> (50%); 1/6 (50%)	Vertigo		<b>11/5</b> (78.57%); <b>3/6</b> (21.43%)
<b>2/4</b> (100%)	Mind concentration		<b>12/5</b> (85.71%); <b>2/6</b> (14.29%)
<b>2/6</b> (100%)	Work skill		<b>7/5</b> (50%); <b>7/6</b> (50%)
Score sum between 60 and 63	TOTAL		Score sum between 59 and 69
Table 2C		Grade III: 4SC out of 482 patients	

vPTA (9 into SP) (3.42%)			no-vPTA (22 into SP) (10.09%)
<b>Patients</b> /scores from 7 to 10 (%)			<b>Patients</b> /scores from 7 to 10 (%)
<b>2/7</b> (22.22%); 5/8 (55.56%); 2/9 (22.22%)	Diplopia		<b>18/7</b> (81.81%); <b>4/8</b> (18.19%)
<b>9/9</b> (100%)	Fatigue		<b>22/9</b> (100%)
<b>7/7</b> (77.78%); 2/8 (22.22%)	Headache		<b>10/7</b> (45.45%); <b>7/8</b> (31.82%); <b>5/9</b> (22.73%)
<b>9/10</b> (100%)	Upper limb mobility		<b>22/10</b> (100%)
<b>9/10</b> (100%)	Lower limb mobility		<b>22/10</b> (100%)
<b>6/7</b> (66.67%); 3/8 (33.33%)	Thermic sensibility		<b>11/7</b> (50.00%); <b>8/8</b> (36.36%); <b>3/9</b> (13.64%)
<b>5/7</b> (55.56%); <b>4/9</b> (44.44%)	Bladder control		<b>10/7</b> (45.45%); <b>11/8</b> (50.00%); <b>1/10</b> (4.55%)
<b>3/7</b> (33.33%); <b>3/8</b> (33.33%); <b>3/9</b> (3.33%)	Balance coordination		<b>6/7</b> (27.27%); <b>12/8</b> (54.55%); <b>4/9</b> (18.18%)
<b>6/7</b> (66.67%); <b>2/8</b> (22.22%); <b>1/9</b> (11.11%)	Quality of sleep		<b>7/7</b> (31.82%); <b>10/8</b> (45.45%); <b>5/9</b> (22.73%)
<b>7/7</b> (77.78%); <b>2/8</b> (22.22%)	Vertigo		<b>10/7</b> (45.45%); <b>10/8</b> (45.45%); <b>2/9</b> (9.10%)
<b>9/8</b> (100%)	Mind concentration		<b>10/8</b> (45.45%); <b>12/9</b> (54.55%)
<b>9/8</b> (100%)	Work skill		<b>22/9</b> (100%)
Score sum between 94 and 105	TOTAL		Score sum between 95 and 110

4SC: self-symptom severity score classification; vPTA: vein angioplasty; MS: multiple sclerosis; RR: relapsing-remitting; SP: secondary progressive.

home and outdoors. In general, life quality had worsened and assistance was indispensable (Table 2C). The clinical situation was confirmed by the neurologist physician.

Data were performed and expressed as mean (average score in vPTA group *versus* control no-vPTA group and statistical analyses were obtained with SAS (Statistical Analysis System) software aimed for statistical and mathematical analysis (Tables 3A-C).

A paper by Confavreux<sup>36</sup> may be a useful comparison landmark for this work since it contributes to the evolution of MS and span of the disease too.

## Results

Among the totality of the RR population that was observed for CCSVI, all had Duplex outflow issues, hemodynamic or morphological disfunctions, such as internal jugular stenosis, hypoplasia or valve hypomobility at the brachiocephalic junction. In most cases (91% of the examined) all issues were present and, initially, they principally interested the left internal jugular vein. In 313 (65%) patients the venous outflow furtherly worsened because of the vertebral vein plex reflux and azygous vein abnormalities (mainly stenosis and coiling), as subsequently confirmed during the phlebogram investigation and eventual vPTA.

Concomitant significant Duplex evidences, also regarding right internal jugular vein issues and right vertebral plex reflux, were present only in 101 patients (21%) and these observations also were confirmed by phlebograms.

In contrast, Duplex exams carried out on the 9 RR post vPTA patients that, with time evolved into SP, severe vein outflow issues were principally detected at the right venous internal jugular and vertebral plex outflow with the left side remaining unchanged.

Moreover, posture and walking disabilities that necessarily required assistance or devices changed along with the severity of the disease. Figures 1 to 4 and tables 4 to 7 help understand the MS evolution from year 5 to year 10. Both the given EDSS and the self-declared 4SC values magnify statistically significant changes in the lapse included between years 6-7 to years 8-9, as described. This peculiarity also developed muscle hyperplasia at the neck with secondary extrinsic muscle compression (principally from the omohyoid muscle) mainly on the right jugular vein outflow. At the "turtle-neck" maneuver, vein compression was almost immediate and complete and

**Table 3. A) Self-symptom severity score classification - grade I: scores from 0 to 4. (\*) Independent samples T test with the assumption that one group has a different variance than the other. Considering the grade I total score section, the less severe, all the 12 most usually complained symptoms are significantly more elevated in patients treated with vein angioplasty than in non-treated patients. B) Self-symptom severity score classification - grade II: scores from 5 to 6. The number of patients who developed grade II intermediate of relapsing-remitting multiple sclerosis displaying different scores for each symptom is reported. The number of vein angioplasty patients is only 2, whereas no vein angioplasty patients are 9, making not applicable statistic comparison. The resulting information is only "qualitative". The quality of life is more elevated in vein angioplasty patients than in no vein angioplasty patients regarding the following symptoms: headache, thermic sensibility, quality of sleep, vertigo, mind concentration and work**

Average score in vPTA Group versus Control (no-vPTA) Group				
	vPTA Group (253 patients)	no-vPTA Group (182 patients)	T test with Satterthwaite Method (*)	P-values
Diplopia	0,0	2,6	t=31,23	<0,0001
Fatigue	1,0	3,9	t=100,60	<0,0001
Headache	0,0	2,1	t=112,00	<0,0001
Upper Limb Mobility	1,1	2,6	t=23,68	<0,0001
Lower Limb Mobility	1,1	2,6	t=23,68	<0,0001
Thermic Sensibility	1,0	3,1	t=30,54	<0,0001
Bladder Control	1,0	3,4	t=35,57	<0,0001
Balance Coordination	1,0	2,4	t=37,11	<0,0001
Quality of Sleep	1,0	3,1	t=30,68	<0,0001
Vertigo	0,3	2,1	t=33,98	<0,0001
Mind Concentration	0,0	3,7	t=84,32	<0,0001
Work Skill	1,2	3,3	t=40,69	<0,0001

Average score in vPTA Group versus Control (no-vPTA) Group			
	vPTA Group (2 patients)	no-vPTA Group (14 patients)	vPTA is better (*)
Diplopia	5,0	5,3	*
Fatigue	5,5	5,5	
Headache	5,0	5,2	*
Upper Limb Mobility	6,0	5,1	
Lower Limb Mobility	6,0	5,1	
Thermic Sensibility	5,0	5,1	*
Bladder Control	5,5	5,3	
Balance Coordination	5,0	5,0	
Quality of Sleep	5,0	5,0	
Vertigo	5,5	5,2	
Mind Concentration	5,0	5,1	*
Work Skill	6,0	5,5	

Average score in vPTA Group versus Control (no-vPTA) Group			
	vPTA Group (9 patients)	no-vPTA Group (22 patients)	vPTA is better (*)
Diplopia	8,0	7,2	
Fatigue	9,0	9,0	
Headache	7,2	7,8	*
Upper Limb Mobility	10,0	10,0	
Lower Limb Mobility	10,0	10,0	
Thermic Sensibility	7,3	7,6	*
Bladder Control	7,9	7,6	
Balance Coordination	8,0	7,9	
Quality of Sleep	7,4	7,9	*
Vertigo	7,2	7,6	*
Mind Concentration	8,0	8,5	*
Work Skill	8,0	9,0	*

4SC: self-symptom severity score classification; vPTA: vein angioplasty; MS: multiple sclerosis; RR: relapsing-remitting; SP: secondary progressive.

very similar with what occurred when using a walking stick or crouch. Casually, all nine patients were right-handed and admitted feeling stronger when leaning on the right side and consequently probably facilitated right side muscular neck hypertrophy.

Among the 22 no-vPTA Patients, all showed Duplex jugular vein issues that severely concerned the right side with the left venous outflow issues, once again, similar to previous exams. Once more, the evolution from RR to SP coupled with a worsened right jugular vein outflow insufficiency, in addition to the already mentioned muscle hypertrophy and compression.

Clinically, and in a period of 10 years of Duplex for CCSVI outflow issues, among the 264 vPTA treated patients, 9 (3.42%) matched with the more severe grade III classification, where fatigue, upper and lower limb mobility, bladder control, mind concentration and working skills were the most consistent problems. Only 2 patients (0.75%) placed themselves in the intermediate grade II. All the remaining 253 (95.83%) still classified as RR and living a satisfactory QoL condition on the basis of symptoms and disabilities similar to those resulted in 2015 at mid-term check and still in the grade I classification. (Table 2).

Similarly, in the control group of 218 no-vPTA patients, 22 (10.09%) recognized by their physicians as SP classified themselves into grade III of the 4SC. Once again fatigue, limb mobility, bladder control, stability, working capacity and mind concentration resulted the most important issues. Among the remaining population, 14 (6.42%) were included in the intermediate grade II and the remaining 182 (83.49%) were still in grade I of the 4SC.

In both groups, the change of the clinical course from RR into SP caused patients to develop mobility worsening that required aids. On the basis of our 10-years series, it appears that vPTA allows for a longer interval, for a better QoL and longer-lasting benefits.

Moreover, the patients helped to develop self-observation scores, not limiting only to mobility but also to other life-influencing issues.

## Discussion

This case-control study is an *excursus* review that combines together vascular issues, symptom evolution and a progressive neurologic disease in an initially homogeneous RRMS population through 10-years with or without vPTA treatment for MS. Furthermore, hints to be applied for rehabilitation programs and use of devices may be achieved here. Muscular extrinsic

secondary compression should be avoided as most possible and postural correction carefully detected or improved.<sup>37</sup>

Quality of life is not just a question of mobility, but also dependency for more rehab and occupational therapy that altogether mean costs, both individual and to the healthcare system. Ten years of follow-up, for a consistent number of patients, regarding CCSVI vein abnormalities and

disabilities, have bridged a series of gaps inside a progressive neurologic disease. Starting from the initially less severe disease at the RR phase, the results encourage the opportunity of performing a CCSVI Duplex imaging exam as a standard, regardless of the MS disease being suspected or confirmed, since it may be useful to identify the subset of MS patients with CCSVI that could benefit from angioplasty.<sup>38</sup>

**Table 4. Vein angioplasty group (vPTA) (9 patients) - grade III. Neurological evaluation Kurtzke expanded disability status scale (EDSS) and self-symptom severity score classification (4SC) average score and p values change from 5 years to 6-7 years. The change from 5 years to 6-7 years is not significant (with alpha level = 0,05), both for neurological evaluation Kurtzke expanded disability status scale and self-symptom severity score classification.**

	Average score in vPTA group (9 patients) - grade III			p values
	5 years	6-7 years	T test with pooled method (*)	
EDSS	3,1	3,5	t=-1,67	0,1137
4SC	5,7	6,6	t=-2,00	0,0628

(\*) Dependent samples T test with the assumption that groups have equal variance.

**Table 5. Vein angioplasty group (vPTA) (9 patients) - grade III. Neurological evaluation Kurtzke expanded disability status scale (EDSS) and self-symptom severity score classification (4SC) average score and p values change from 6-7 years to 7-8 years. Scores for both neurological evaluation Kurtzke expanded disability status scale and self-symptom severity score classification in 7-8 years are significantly different (with alpha level = 0,05) from 6-7 years evaluation.**

	Average score in vPTA group (9 patients) - grade III			p values
	6-7 years	7-8 years	T test with pooled method (*)	
EDSS	3,5	4,2	t=-2,67	0,0169
4SC	6,6	7,6	t=-2,92	0,0100

(\*) Dependent samples T test with the assumption that groups have equal variance.

**Table 6. Vein angioplasty group (vPTA) (9 patients) - grade III. Neurological evaluation Kurtzke expanded disability status scale (EDSS) and self-symptom severity score classification (4SC) average score and p values change from 7-8 years to 8-9 years. Scores for both neurological evaluation Kurtzke expanded disability status scale and self-symptom severity score classification in 8-9 years are significantly different (with alpha level = 0,05) from 7-8 years evaluation.**

	Average score in vPTA group (9 patients) - grade III			p values
	7-8 years	8-9 years	T test with pooled method (*)	
EDSS	4,2	4,8	t=-2,41	0,0282
4SC	7,6	8,2	t=-2,35	0,0317

(\*) Dependent samples T test with the assumption that groups have equal variance.

**Table 7. Vein angioplasty group (vPTE) (9 patients) - grade III. Neurological evaluation Kurtzke expanded disability status scale (EDSS) and self-symptom severity score classification (4SC) average score and p values change from 8-9 years to 10 years (final). The change from 8-9 years to 10 years is not significant (with alpha level = 0,05), both for neurological evaluation Kurtzke expanded disability status scale and self-symptom severity score classification**

	Average score in vPTA group (9 patients) - grade III			p values
	8-9 years	10 years (final)	T test with pooled method (*)	
EDSS	4,8	5,2	t=-2,41	0,2320
4SC	8,2	8,6	t=1,01	0,3256

(\*) Dependent samples T test with the assumption that groups have equal variance.

## Conclusions

It is still not certain if all MS patients that undergo to vPTA to correct CCSVI receive the same benefits from this treatment, but apparently the progression is slower and in this series patients' 4SC grade marks are better. One firm observation in our series was that vPTA, meant to correct CCSVI, resulted to be safe as already described by other authors,<sup>39-42</sup> since no issues were detected after this procedure.

Our conclusion possibly contributes to answer the so-far unanswered key question: "does percutaneous venoplasty make a difference in relieving the symptoms of multiple sclerosis by improving cerebrospinal venous drainage and clinical symptoms"? We think so.

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