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Assessment of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis by a Morphological-Hemodynamic-Map software

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Aim. **The aim of the present study was to determine a Echo-Color-Doppler (ECD) data analysis algorithm for patients with multiple sclerosis (MS) affected by chronic cerebrospinal venous insufficiency (CCSVI) by using a morphological-hemodynamic-map (MEM-net). The CCSVI is a new nosological vascular pattern that has been recently founded also in MS patients.**

Methods. **We investigated 552 MS patients (mean age: 43±10 years) by Echo-Color-Doppler (ECD, MyLab Vinco System, Esaote), out of which 333 females (60%) and 219 males (40%). The identification of CCSVI by ECD examination was obtained following Zamboni's criteria. The ECD data were analysed by MEM-net software (www.mem-net.it), which made possible an on-line diagnosis of positive (83%) or negative (17%) CCSVI patients.**

Results. **We classified CCSVI in three different types by identifying a new hemodynamic parameter the "venous compression". Type-1 with intravenous block (17%), type-2 with extravenous compression (4%) and type-3 with both conditions (79%).**

Conclusion. **The results provide the hemodynamic basis for a new CCSVI classification, which may lead to a better optimization of individual treatment.**

KEY WORDS: Venous insufficiency - Multiple sclerosis - Compression bandages.

Multiple sclerosis (MS), the most common neurological disorder in young adults, is traditionally considered to have autoimmune determinants.[1] The multistep mechanism of the disease involves inflammation, demyelination, and neurodegeneration of the central nervous system.[1-3] Interestingly, from the time of the first histological description by Charcot, MS plaques are known to be venocentric.[2, 4] Both magnetic resonance imaging (MRI) venography [5-9] and *post-mortem* studies show a central vein oriented on the long axis of the inflammatory lesion.

In addition, as in several neurodegenerative disorders, the brain and spinal cord of MS patients contain abnormally high levels of redox-active metals, particularly iron,[10] documented by advanced MRI [1, 12] and enhanced histo-chemical methods.[13, 14]

There are several different types [1, 2, 15] of MS, based on clinical characteristics: relapsing remitting MS (RRMS, 85%);[16] secondary progressive MS [SPMS, 15%]);[15, 16] primary progressive MS (PPMS, 5%).[17] RRMS is the most common form of the disease. Patients affected by this form tend to experience an attack or series of attacks (exacerbations) followed by complete or partial remission.[16] SPMS begins with RRMS, it is chronic and progressive. There are no real periods of remission, only breaks in the attacks' duration with no sustained recovery from symptoms.[15, 16] PPMS is characterized by a

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gradual clinical decline with no periods of remission from the outset.[17] There are several diagnostic tools to identify the different MS types.[1, 2, 18-20] MRI of the brain and spine shows areas of demyelination (lesions or plaques) in the absence or in the presence of gadolinium.[21, 22] Analysis of cerebrospinal fluid may provide evidence of chronic inflammation of the central nervous system by showing oligoclonal bands of IgG,[23] while evoked potentials study putative demyelination of the optic and sensory nerves.[24] A clear demonstration of a topographic correspondence between Multiple Sclerosis plaques and the cerebral venous system has been shown by Magnetic Resonance Venography (MRV) [7, 25] and *post-mortem* studies.[26]

Such new nosological vascular pattern, defined as chronic cerebrospinal venous insufficiency (CCSVI), is strongly associated with MS.[27] CCSVI is characterized by multiple stenosis/obstructions affecting the principal extracranial outflow pathways of the cerebrospinal venous system, the internal jugular veins (IJVs) and the azygos vein (AZY), distributed in four main hemodynamic patterns.[28, 29] Furthermore, CCSVI determines significant changes in cerebral venous hemodynamic, with a very high incidence of reflux in both intra- and extracranial venous segments as well as loss of the postural regulation of cerebral venous outflow.[29-32] Recently, Zamboni suggested five Echo-Color-Doppler (ECD) venous criteria that characterize this syndrome: 1) reflux constantly present in an outflow pathway; 2) reflux propagated upward to the deep cerebral veins (DCVs), including internal cerebral vein, basal vein, Galen vein; 3) evidence of IJVs stenosis; 4) flow not Doppler detectable in the IJVs and vertebral veins (VVs); 5) negative difference in cross sectional area of the IJV (CSA) assessed in supine and standing posture (0° and 90°) in the IJV (ΔCSA).[28] The presence of two of them is enough to diagnose CCSVI.

We created a software to collect morphologi-

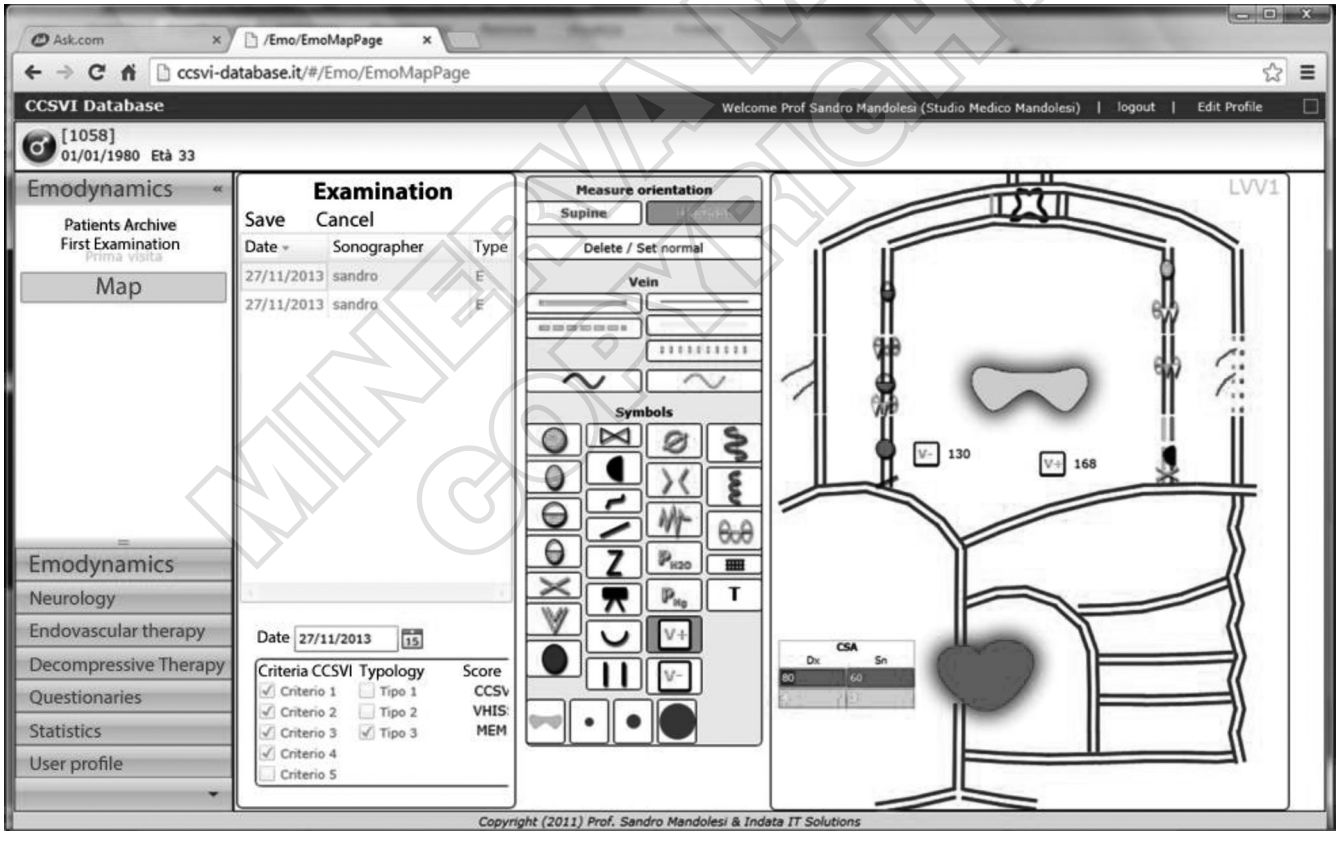

Figure 1.—Morphological hemodynamic map (MEM) scheme representing pattern of ECD venous cerebrospinal drainage, CCSVI types, hemodynamic severity score and patient data.

cal venous anomalies and hemodynamic ECD data named Morphological Hemodynamic Map (www.mem-net.it, Figure 1). The present study was designed to determine an algorithm for data analysis of patients with MS and CCSVI, following Zamboni's ultrasound criteria,[27-31] by using such hemodynamic morphological map (MEM-net). This study provides the hemodynamic basis for a new CCSVI classification.

Materials and methods

We studied with ECD (Esaote unit Mylab-Vinco) 552 patients affected by Multiple Sclerosis (MS) according to the revised McDonald's criteria [9-10), of which 333 were females (60%) and 219 males (40%), aged 43±10 years (Table I). The patients were recruited in the Department of Cardiovascular, Respiratory, Nephrology, and Geriatric Sciences in the "Umberto I" Polyclinic of Rome, "Sapienza" University, from 2009 to 2011. The ECD data were analyzed using the MEM-net algorithm. Furthermore, the patients were divided into three score groups, according to Expanded Disability Status Scale (EDSS),[32] 0-3 (low), 4-6 (intermediate) and 7-9 (high). Written informed consent was obtained from all subjects.

Echo-Color Doppler assessment of cerebral venous hemodynamics

The patients underwent a non-invasive study of cerebral venous return. A combined trans-cranial and extra-cranial ECD (MyLab Vinco ECD System) equipped with 2.5 and 7.5-10 Mhz probes (Esaote Biosound Genoa, Italy) provided valid measures of venous hemodynamic (VH) parameters enabling an assessment of CCSVI cerebral venous return. The subjects were investigated in both supine and standing positions (0° and 90°) in consideration of the postural effect on the main route of cerebral outflow. We focused on the detection of five anomalous VH patterns affecting cerebral venous return according to the Zamboni's criteria.[27-31]

— Criterion 1 (C1): reflux in the IJVs and/or VVs at 0° and 90°. According to a recent study on reflux time cut-off values [27], we considered reflux a flow reversal from its physiological direction for a duration of 0.88 s. Flow was never assessed in a forced condition such as the Valsalva maneuver. The presence of reflux was detected in the four extra-cranial venous drainage pathways with the body positioned at 0° and 90°, respectively.

— Criterion 2 (C2): reflux in the DCVs (internal cerebral vein, basal vein of Rosenthal, great vein of Galen). Physiological intracranial venous flow is mono-directional, ultrasound trans-cranial investigation assessed the presence of reflux in at least one of the DCVs. Patients were examined in both sitting and supine positions, and the venous flow was elicited by inviting the subject to breath and setting the reflux time to a value of 0.5 s.

— Criterion 3 (C3): evidence of IJV stenosis. The presence of venous imaging stenosis was assessed by means of a complete ECD high resolution B-mode exploration of the cervical vessels, and measurement of the CSA of the IJV. A CSA of 0.3 cm^2, never measured in normal subjects, was taken as reference value.

TABLE I.—*Clinical severity vs. EDSS and disease duration.*

ALL PATIENTS 552 (100%)		TOTAL MS 552 (100%)	RR-MS 365 (66%)	SP-MS 130 (24%)	PP-MS (57 (10%)	P
PATIENTS' SEX female + male (% F + % M)		333+219 (60%+40%)	222+143 (61%+39%)	77+53 (59%+41%)	34+23 (60%+40%)	NS
AGE in years (mean ± SD)		43 ± 10	41±10	47±9	45±11	P<0.001
DISEASE DURATION in years (mean±SD)		10±7	9±7	13±9	12±8	P<0.001
EDSS total score	(0~3)	201 (36%)	162 (44%)	27 (21%)	12 (21%)	P<0.001
	(4~6)	279 (51%)	167 (46%)	78 (60%)	34 (60%)	
	(7~9)	72 (13%)	36 (10%)	25 (19%)	11 (19%)	

data about 552 MS patients, CCSVI positive and CCSVI negative (number of signs/symptoms for patient)

— Criterion 4 (C4): flow not Doppler detectable and not visible in the IJVs and/or VVs. Lack of a Doppler detectable venous flow in the IJVs and/or VVs despite numerous deep inspirations, with the head positioned at 0° and 90° in the four extra-cranial venous drainage pathways. The PRF is regulated to 0.7 and Doppler angle to 60% and the Doppler outflow time is more than the stop flow time (Figure 2).

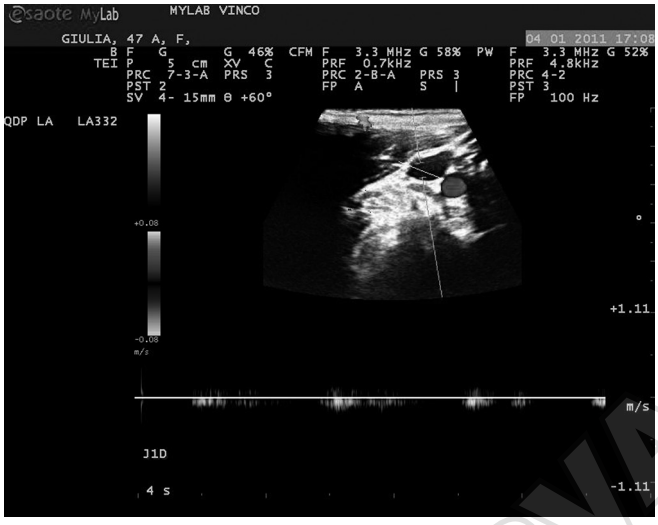

Figure 2.—Representative hemodynamic block of the J3 right internal jugular vein (intravenous block).

— Criterion 5 (C5): reverted postural control of the main cerebral venous outflow pathway ΔCSA in the IJVs, obtained by subtracting the CSA measured in the supine from that in the sitting position, is a positive value in normal subjects. We assessed the occurrence of a negative ΔCSA value, representing the loss of postural control of the predominant outflow route in the supine position.

Beside the Zamboni's criteria our population was studied using new hemodynamic patterns to complete the evaluation of the cerebro-spinal venous drainage: 2) the venous compression of the IJVs and/or VVs in supine and/or standing posture. We define venous compression as a normal vein not visible with ultrasound, because collapsed, which may expand with neck position changes and/or Valsalva maneuver (Figure 3). Such a vein presents a block of blood flow; 2) the hemodynamic stenosis in the IJVs and/or VVs is defined when the venous flow velocity is equal or higher than 150 cm/sec with 60° Doppler angle (Figure 4).

In all our ECD assessments we performed the following ECD dynamic tests: Valsalva's maneuver, performed by moderately forceful attempted exhalation against a closed airway, usually done by closing one's mouth and pinching one's nose shut; neck movements, on right, on left rotation and anterior/posterior intrusion of the neck

According to these new hemodynamic param-

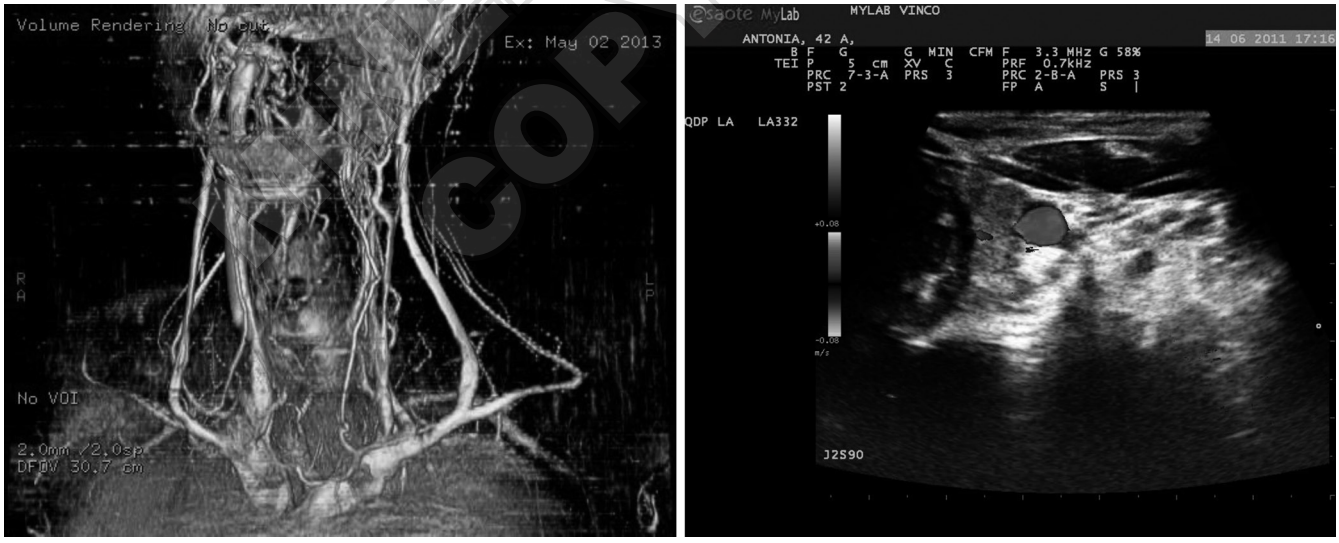

Figure 3.—Representative venous MRI 3T and ECD of left IJV Compression. The left panel shows the MRI of the internal jugular veins where only the right jugular is visible. The right panel shows compression of the left internal jugular vein detected by ECD.

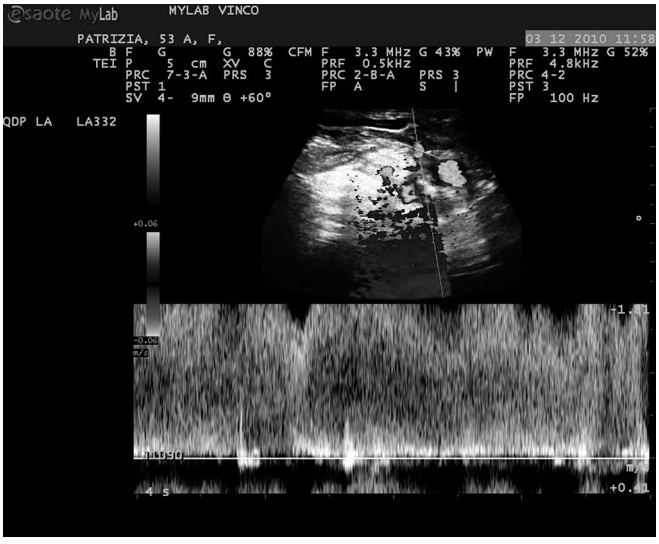

Figure 4.—Hemodynamic stenosis of the right internal jugular vein where it can be noted that flow velocity is greater than 200 cm/s

eters, we classified our patient population in three different CCSVI types. Block and/or stenosis and/or reflux of the IJVs and DCVs as type-1; compression of the IJV and/or VV not visible as type-2. The mixed form composed by patients with block and/or stenosis of IJVs and/or reflux of the IJVs and DCVs and compression of the IJVs and/or VVs not visible as type-3. These parameters were used to draw up our algorithm.

Our center designed and developed for the first time the morphological hemodynamic map (MEM) of the CCSVI. The MEM is made by a scheme reproducing the intracranial and extra-cranial venous circulation. The operator can insert in a few seconds different symbols to define the aforementioned hemodynamic conditions and also venous anomalies including hypo-plasic veins, veins with stiffness of walls (not compliant), septum, membrane, web, annulus, twist and valve stiffness. The collected ECD data were analyzed by MEM-net software (www.mem-net.it), which includes the data analysis algorithm.

Statistical analysis

All data were analyzed by SPSS software with a stratified data description for numeric and non-numeric variables. Statistical significance "between" and "within" groups was calculated on continuous variables by the analysis of variance (ANOVA) to test the equality of means. The Chi-square Yates corrected test was used for non-continuous variables by Statcalc and Analysis programs from Epi-Info. A P value <0.05 was considered significant, and 95% confidence intervals were also calculated.

Results

457 patients out of 552 analysed (83%) were positive to CCSVI according to Zamboni's criteria, of which 273 were females (60 %) and 184 males (40%); mean age was 43±10 years. In these patients, the percentages of the five Zamboni's criteria were the following: 48% (C1); 56% (C2); 74% (C3); 62% (C4) and 13% (C5), respectively.

The other 95 patients (17% of total sample) were negative to CCSVI, of which 60 females (63%) and 35 males (37%); mean age was 41±11 years. The percentages in these patients of the five Zamboni's criteria were 36% (C1); 16% (C2); 14% (C3); 21% (C4) and 1% (C5), respectively.

In Table I we have stratified the CCSVI positive subjects according to their clinical characteristics into relapsing-remitting (RR, 66%), secondary progressive (SP, 23%) and primary progressive (PP, 11%) patients. We found statistically significant differences between these three groups of patients. RR patients were younger than others (P<0.001) and disease duration was shorter (P<0.001).

According to the EDSS total score, our patient sample was divided into three severity groups: low severity (0 to 3 points); middle severity (4 to 6 points); high severity (7 to 9 points). If we analyse the 0-3 points category, the percentage of patients with RR-MS was double than that of patients with SP-MS or PP-MS. If we analyse the 4-6 points category, the percentage of patients with RR-MS was one third less than that of patients with SP-MS or PP-MS. If we analyse the 7-9 points category, the percentage of patients with RR-MS was one half less than that of patients with SP-MS or PP-MS.

The statistical significant differences showed in EDSS total score groups were as follows: 89% of RR-MS patients presented a low-middle (0-6) severity EDSS score, whereas 85% of SP had a middle-high (4-9) severity EDSS score (P<0.001). At the same time, 82% of PP-MS patients had a middle-high (4-9) severity EDSS score (P<0.001).

We also stratified CCSVI negative subjects according to their clinical characteristics into Relapsing-Remitting (RR, 66%), Secondary Progressive (SP-MS, 27%), and Primary Progressive (PP-MS, 7%) patients. The stratification by sex showed a distribution having a statistically significant difference (P<0.05).

In Table II we stratified CCSVI positive and negative subjects according to Zamboni's criteria. There were no statistically significant differences between these parameters after stratification.

In Table III, according to the implementation of our new hemodynamic parameters, we stratified the CCSVI positive subjects into type-1 (17%), type-2 (4%) and type-3 (79%).

While high EDSS scores are basically the same in the CCSVI positive patients, there are differences into low- and middle-EDSS scores in the same patients. These data show statistically significant differences with P<0.01 (Chi-square=9.86 with 2 df).

We also stratified CCSVI negative subjects according to their four types as type-0 (41%), type-1 (43%), type-2 (16%) and type-3 (0%), respectively. The percentage of male patients with PP-MS was higher than that of female patients with SP-MS or RR-MS. However, we could not analyze the table because the sample of patients with PP-MS was too small. We found statistically significant differences between these four groups and middle severity (4 to 6 points) EDSS (P<0.01).

Discussion

Up to date the CCSVI was divided only in positive and negative. The present study proposes for the first time a new classification of Chronic Cerebro-Spinal Venous Insufficiency in patients with Multiple Sclerosis using a new algorithm applied to morphological hemodynamic map.

On line data collection allowed CCSVI diagnosis, VHISS Zamboni's score, and the classification of CCSVI into three types. We have indeed identified patients with intravenous lesions (type-1), extra-venous compressions (type-2) and with both conditions (type-3). Our study demonstrates the hemodynamic relevance of the extra-cranial venous compressions in the different postures.

TABLE II.—*CCSVI Zamboni's criteria vs EDSS and disease duration.*

ALL PATIENTS 552 (100%)		PATIENTS 552 (100%)	C_1 255 (46%)	C_2 271 (49%)	C_3 351 (64%)	C_4 305 (55%)	C_5 58 (10%)	p
PATIENTS' SEX female+male (% F+% M)		333+219 (60%+40%)	150+105 (59%+41%)	166+105 (61%+39%)	211+140 (60%+40%)	183+122 (60%+40%)	31+27 (53%+47%)	NS
AGE in years (mean±SD)		43±10	43±10	43±10	42±10	44±10	44±9	NS
DISEASE DURATION in years (mean±SD)		10±7	11±7	10±8	10±7	12±8	12±7	NS
EDSS	(0~3)	201 (36%)	69 (34%)	113 (56%)	129 (64%)	98 (49%)	14 (7%)	---
	(4~6)	279 (51%)	143 (51%)	125 (45%)	177 (63%)	155 (56%)	28 (10%)	
	(7~9)	72 (13%)	43 (17%)	33 (12%)	45 (13%)	52 (17%)	16 (28%)	
CCSVI (POSITIVE)		PATIENTS 457 (83%)	C_1 221 (48%)	C_2 256(56%)	C_3 338 (74%)	C_4 285 (62%)	C_5 57 (13%)	---
PATIENTS' SEX female+male (% F+% M)		273+184 (60+40%)	127+94 (58+42%)	154+102 (60+40%)	205+133 (61+39%)	170+115 (60+40%)	30+27 (53+47%)	NS
AGE in years (mean±SD)		43±10	44±10	44±10	43±10	44±10	44±10	NS
DISEASE DURATION in years (mean±SD)		11±8	11±8	10±8	10±7	12±8	13±8	NS
EDSS	(0~3)	115 (34%)	60 (27%)	102 (40%)	117 (35%)	93 (33%)	13 (23%)	---
	(4~6)	233 (51%)	118 (53%)	121 (47%)	176 (52%)	142 (50%)	28 (49%)	
	(7~9)	69 (55%)	43 (20%)	33 (13%)	45 (13%)	50 (17%)	16 (28%)	

Data about 552 MS patients, CCSVI positive and CCSVI negative (number of signs/symptoms for patient)

TABLE III.—*CCSVI types vs Zamboni's criteria, EDSS and disease duration.*

ALL PATIENTS 552 (100%)		Type_0 39 (7%)	Type_1 120 (22%)	Type_2 31 (6%)	Type_3 362 (65%)	P
PATIENTS' SEX			7			NS
female+male		25+14	9+41	21+10	208+154	
(% F+% M)		(64+36%)	(66+34%)	(68+32%)	(58+42%)	
AGE in years						
(mean±SD)		42±11	42±10	41±10	43±10	NS
DISEASE DURATION						
in years						trend
(mean±SD)		7±4	10±7	11±9	11±8	P=0.07
EDSS	(0~3)	13 (33%)	54 (33%)	14 (45%)	120 (33%)	P<0.05
	(4~6)	25 (64%)	55 (64%)	12 (39%)	187 (52%)	
	(7~9)	1 (3%)	11 (3%)	5 (16%)	55 (15%)	
POSITIVE CCSVI 457 (83%)		type_0 0 (0%)	type_1 79 (17%)	type_2 16 (4%)	type_3 362 (79%)	
PATIENTS' SEX						
female+male		0+0	54+25	11+5	208+154	NS
(% F+% M)		(%+%)	(68%+32%)	(69%+31%)	(57%+43%)	
AGE in years						
(mean±SD)		0±0	43±10	43±9	43±10	NS
DISEASE DURATION						
in years						
(mean±SD)		0±0	10±8	11±7	11±8	NS
EDSS	(0~3)	0 (0%)	32 (40%)	3 (19%)	120 (33%)	P<0.01
	(4~6)	0 (0%)	36 (46%)	10 (62%)	187 (52%)	
	(7~9)	0 (0%)	11 (14%)	3 (19%)	55 (15%)	
ALL PATIENTS 552 (100%) CRITERIA	C_1 255 (46%)	24 (4%)	54 (10%)	19 (3%)	159 (29%)	NS
	C_2 271 (49%)	3 (1%)	52 (9%)	14 (3%)	202 (37%)	
	C_3 351 (64%)	0 (0%)	63 (11%)	0 (0%)	287 (51%)	
	C_4 305 (55%)	1 (0%)	50 (9%)	9 (2%)	237 (43%)	
	C_5 58 (10%)	0 (0%)	10 (2%)	6 (1%)	42 (8%)	

Data about 552 MS patients, CCSVI positive and CCSVI negative (number of signs/symptoms for patient)

The MEM-net software simplifies data recording while reducing the risk of human error making possible the standardization of the ECD report as well as the follow-up of patients undergoing different treatments. Furthermore, the system allows a thorough statistical and epidemiological analysis, and offers an easy and understandable presentation to the patient of his/her vascular condition.

This new CCSVI classification may help us either for a more accurate stratification of our MS population for further studies, or to understand the most appropriate treatment for these different types of patients. Our results allowed evaluating the incidence of type-1, type-2 and type-3. We hope that the proposed classification of CCSVI will be implemented in other clinical studies dealing with similar patient populations.

The analysis of the positive and the negative CCSVI sample data, obtained by applying our algorithm, shows the presence of a fourth type of CCSVI. Whereas type-0 is never present in patients with positive CCSVI, it is detectable in those with negative CCSVI. type-0 is the hemodynamic condition not covered by the algorithm. In negative CCSVI patients, it can be noted that type-3 is never occurring due to the fact that this type should include patients with two different hemodynamic conditions corresponding to two different Zamboni's criteria. However, since by definition these are patients with one single criterion this condition simply cannot occur.

Further studies are needed to further validate this diagnostic tool. To this aim our group is performing additional investigations to determine whether this

system may provide a better classification of patients with MS and CCSVI as well as the indication of different treatments. CCSVI identified by Zamboni was treated by using venous angioplasty obtaining positive results on MS clinical signs in over 70% of patients in the first study. It was just following the high percentage of failures (almost 30%) that we felt motivated to investigate whether - in addition to intravenous blocks identified by Zamboni - there could be different hemodynamic conditions, yet neglected, that could justify the lack of results.[33] The identification of a block to the brain venous drainage not only intravenous but also extravenous allowed realizing that its cause could be not only vascular but also mechanical-postural. The angioplasty of a vein with a block, caused by external compression of the vessel, may yield no results because the cause, external to the vessel, cannot be resolved by its dilation.

In this regard we may speculate that type-1 should be treated with angioplasty, type-2 should be more suitable for a specific physiotherapy approach or surgical interventions to accomplish vessel decompression,[34] whereas type-3 may receive both treatments.

Riassunto

Valutazione dell'insufficienza venosa cronica cerebrospinale mediante il programma computerizzato di mappa emodinamica morfologica

Obiettivo. L'obiettivo del presente studio è stato quello di determinare un algoritmo di analisi dei dati EcoColor-Dopper (ECD) di pazienti con sclerosi multipla (SM) affetti da insufficienza venosa cronica cerebrospinale (CCSVI) utilizzando una mappa emodinamica morfologica computerizzata (MEM - net). La CCSVI è una nuova condizione nosologica vascolare che è stata recentemente evidenziata anche nei pazienti con SM.

Metodi. Abbiamo studiato 552 pazienti con sclerosi multipla (età media: 43±10 anni) con Eco-Color-Doppler MyLab Vinco sistema, Esaote, di cui 333 donne (60%) e 219 maschi (40%). L'identificazione della CCSVI mediante esame ECD è stata ottenuta seguendo i criteri di Zamboni. I dati ECD sono stati analizzati da un software MEM-net (www.mem - net.it), che ha reso possibile una diagnosi online della CCSVI risultata positiva nell'83% e negativa nel 17% dei pazienti.

Risultati. Abbiamo classificato la CCSVI in tre diverse tipologie, avendo individuato un nuovo parametro emodinamico la "compressione venosa ". Il tipo 1 che presenta con blocco endovenoso nel 17% dei casi, il tipo 2 con compressione extravenosa nel 4% e il tipo 3 con entrambe le condizioni (79%).

Conclusioni. I risultati rappresentano la base emodinamica per una nuova classificazione della CCSVI, che può portare a una migliore ottimizzazione del trattamento individuale.

PAROLE CHIAVE: Insufficienza venosa - Sclerosi multipla - Bendaggi compressivi.

References

1. Compston A, Coles A. Multiple sclerosis. Lancet 2002;359:1221-31.
2. Barnett MH, Sutton I. The pathology of multiple sclerosis: a paradigm shift. Curr Opin Neurol 2006;19:242-7.
3. Frohman EM. Multiple sclerosis - the plaque and its pathogenesis. N Engl J Med 2006;354:942-55.
4. Charcot J. Histologie de la sclerose en plaques. Gazette des Hopitaux, Paris 1868;41:554-5
5. Kermode AG, Thompson AJ, Tofts PD, Macmanus G, Kendall BE, Kingsley DPE *et al.* Breakdown of the blood brain barrier precedes symptoms and other MRI signs of new lesions in multiple sclerosis: pathogenetic and clinical implications. Brain 1990;113:1477-89.
6. Kidd D, Barkhof F, McConnell R, Algra PR, Allen IV, Revesz T. Cortical lesions in multiple sclerosis. Brain 1999;122:17-26.
7. Tan IL, van Schijndel RA, Pouwels PJ. MR venography of multiple sclerosis. Am J Neuroradiol 2000;21:1039-42.
8. Fog T. Vessel-plaque relationships and CSF and brain tissue changes in multiple sclerosis. Acta Neurol Scand 1964;40:9-15.
9. Fog T. The topography of plaques in multiple sclerosis with special reference to cerebral plaques. Acta Neurol Scand Suppl 1965;15:1-161.
10. Sayre LM, Moreira PI, Smith MA, Perry G. Metal ions and oxidative protein modification in neurological disease. Ann Ist Super Sanita 2005;41:143-64.
11. Haacke EM, Cheng NYC, Michael JH, Qiang L, Jaladhar N, Robert JO *et al.* Imaging iron stores in the brain using magnetic resonance imaging. Mag Reson Imaging 2005;23:1-25.
12. Tjoia CW, Benedict RH, Weinstock-Guttman B, Fabiano AJ, Bakshi R. MRI T2 hypointensity of the dentate nucleus is related to ambulatory impairment in multiple sclerosis. J Neurol Sci 2005;234:17-24.
13. Sayre LM, Moreira PI, Smith MA, Perry G. Metal ions and oxidative protein modification in neurological disease. Ann Ist Super Sanita 2005;41:143-64.
14. LeVine SM, Chakrabarty A. The role of iron in the pathogenesis of experimental allergic encephalomyelitis and multiple sclerosis. Ann N Y Acad Sci 2004;1012:252-66.
15. Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology 1996;46:907-11.
16. Compston A, Coles A. Multiple sclerosis. Lancet 2008;372:1502-17.
17. Miller DH, Leary SM. Primary-progressive multiple sclerosis. Lancet Neurol 2007;6:903-12.
18. Trojano M, Paolicelli D. The differential diagnosis of multiple sclerosis: classification and clinical features of relapsing and progressive neurological symptoms. Neurol Sci 2001;22:98-102.
19. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD *et al.* Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001;50:121-7.
20. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP *et al.* Diagnostic criteria for multiple sclerosis: 2005 revisions to the McDonald Criteria. Ann. Neurol. 2005;58:840-6.

21. Rashid W, Miller DH. Recent advances in neuroimaging of multiple sclerosis. Semin Neurol 2008;28:46-55.
22. Ge Y, Zohrabian VM, Grossman RI. Seven-Tesla magnetic resonance imaging. New vision of microvascular abnormalities in multiple sclerosis. Arch Neurol 2008;65:812-6.
23. Link H, Huang YM. Oligoclonal bands in multiple sclerosis cerebrospinal fluid: an update on methodology and clinical usefulness. J. Neuroimmunol 2006; 180:17-28.
24. Gronseth GS, Ashman EJ. Practice parameter: the usefulness of evoked potentials in identifying clinically silent lesions in patients with suspected multiple sclerosis (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000;54:1720-5.
25. Hojnacki D, Zamboni P, Lopez-Soriano A, Galeotti R, Menegatti E, Weinstock-Guttman B *et al.* Use of neck magnetic resonance venography, Doppler sonography and selective venography for diagnosis of chronic cerebrospinal venous insufficiency: a pilot study in multiple sclerosis patients and healthy controls. Int Angiol 2010;29:127-39.
26. Geurts JJ, Bö L, Pouwels PJ, Castelijns JA, Polman CH, Barkhof F. Cortical lesions in multiple sclerosis: combined postmortem MR imaging and histopathology Am J Neuroradiol 2005;26:572-7.
27. 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.
28. Zamboni P, Menegatti E. Doppler haemodynamics of vertebral venous return Curr Neurovasc Research 2008;5:260-5.
29. Zamboni P, Menegatti E, Galeotti R, Malagoni AM, Tacconi G, Dall'ara S *et al.* The value of cerebral Doppler venous hemodynamics in the assessment of multiple sclerosis. J Neurol Sci 2009;282:21-27.
30. Zamboni P, Menegatti E, Bartolomei I, Galeotti R, Malagoni AM, Tacconi G, Salvi, F. Intracranial venous hemodynamics in multiple sclerosis. Curr Neurovasc Res 2007;4:252-8.
31. Franceschi C. The unsolved puzzle of multiple sclerosis and venous function. J. Neurol. Neurosurg Psychiatry 2009;80:358.
32. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology1983;33:1444-52.
33. Zamboni, R, Galeotti E, Menegatti, Malagoni AM, Gianesini S, Bartolomei I *et al.* A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency J Vasc Surg 2009; 50:1348-58.
34. Simka M, Majewski M, Fortuna M, Zaniewski M. Internal jugular vein entrapment in a multiple sclerosis patient. Case Rep Surg 2012;2012:293568.

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