

## Analysis of patients with chronic cerebro-spinal venous insufficiency and multiple sclerosis: identification of parameters of clinical severity

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### Abstract

The aims of this study were: i) analysis of clinical severity evolution in multiple sclerosis patients; ii) identification of temporal indicators for clinical worsening. We investigated by echo-color-Doppler (ECD) 789 patients (490 female plus 299 male), aged 45.4 years, with chronic cerebro-spinal venous insufficiency (CCSVI) and multiple sclerosis (MS). All patients tested positive for CCSVI by ECD assessment were divided into three groups, namely: type 1 CCSVI (371) presenting an endo-vascular obstacle to the venous drainage; type 2 CCSVI (40) presenting an extra-vascular obstacle to the venous drainage, for external compression of the vessel; type 3 CCSVI (315) presenting both venous endo-vascular and extra-vascular obstructed drains. We analyzed the morphological and hemodynamic data recorded on computerized map (MEM-net). All data were collected by respecting the Italian Privacy Laws and they are available on the National Epidemiological Observatory on CCSVI website ([www.osservatorioccsvi.org](http://www.osservatorioccsvi.org)). We focused in the three main parameters in all studied patients. First parameter was expanded disability status scale (EDSS) score; second parameter was illness duration; third parameter was CCSVI type. The MS duration values

stratified by EDSS grouped values in CCSVI-type-1 and CCSVI-type-3 patients shows that the differences were statistical significant by Kruskal-Wallis test:  $H=44.2829$ ; degree of freedom=1 for CCSVI-type-1 ( $P<0.001$ ); and  $H=37.3036$ ; degree of freedom=1 for CCSVI-type-3 ( $P<0.001$ ). The present study confirmed and completed scientific literature about relation between CCSVI and MS. On the same time, we found a strong correlation between MS illness duration and severity of EDSS score. In fact there is a clinical severity worsening after 11 years of illness in MS patients with CCSVI type-1 or type-3 ( $P<0.001$ ). These data may suggest the influence of chronic vascular disease on MS. Further searches need in order to learn more about this new aspect in MS etiology.

### Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease with autoimmune pathogenesis that affects the central and peripheral nervous system, causing a variety of clinical signs and symptoms;<sup>1</sup> these are mainly due to scar formation (better known as plaques or lesions) that form in the white matter of the spinal cord and brain.<sup>2,3</sup>

It is estimated that this disease has a prevalence that ranges between 2 and 150 cases per 100,000 individuals.<sup>4</sup> It is believed that multiple sclerosis is an immune-mediated disease caused by a complex interaction between genetic subset of the individual and not yet identified environmental factors.<sup>5</sup>

In 2008, Paolo Zamboni noted that multiple sclerosis is related to altered vasculature where the cervical and thoracic veins are not able to efficiently remove blood from the central nervous system presumably because of stenosis and malformations of jugular veins and azygos.<sup>6-8</sup> Therefore, he identified it as chronic cerebro-spinal venous insufficiency (CCSVI) and diagnosed it on the basis of hemodynamic alterations in relation to postural changes of the extra- and intracranial veins studied by Doppler sonography.<sup>9</sup> According to Zamboni, CCSVI itself would facilitate ferrous cerebral accumulation, to which the body would respond with an immune reaction.<sup>10</sup>

Zamboni discovered this condition in most of people affected with multiple sclerosis, and after performing a surgical procedure to correct the problem stated that 73% of patients had achieved improvements.<sup>7</sup>

The aim of this study was to analyze the evolution of the profiles of clinical severity in a sample of patients with multiple sclerosis and CCSVI with the intent to identify any temporal indicators of clinical worsening.

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### Materials and Methods

We assessed by echo-color-Doppler method (ECD) 789 patients with multiple sclerosis, their diagnosis was made in compliance with McDonald's revised criteria.<sup>11,12</sup> All patients were assessed in the Department of Cardiovascular, Respiratory, Geriatric and Morphologic Sciences of Polyclinic Umberto I of Rome. Among the patients, 490 were female, 299 were male, with an overall mean age of 45.4 years. A total of 728 patients tested positive for CCSVI, while 61 were negative. In addition the morphological and hemodynamic ECD data were analyzed using a computerized map. This is a hemodynamic and morphological map named MEM-net, adopted after the Consensus Conference of the national scientific societies of vascular area to share the symbols and terminology to use for writing MEM-net mapping for a shared and standardized database. This allows us to stratify the data in the different degrees of venous disease, providing answers on the likely impact of CCSVI in MS and the various treatment options. All data were collected by respecting the Italian Privacy Laws and available on the National Epidemiological Observatory on CCSVI website ([www.mem-net.it](http://www.mem-net.it)).

All patients tested positive for CCSVI by ECD assessment were divided into three groups, namely: i) patients affected by type 1 CCSVI (371) presenting an endo-vascular obstacle to the venous drainage, with congenital or acquired abnormalities that restrict and block the drainage of the investigated veins; ii) patients affected by type 2 CCSVI (40) presenting an extra-vascular obstacle to the venous drainage, for external compression of the vessel; iii) patients affected by type 3 CCSVI (315) presenting both venous endo-vascular and extra-vascular obstructed drains.

In order to simplify this classification, we

can say that there is a *hydraulic* CCSVI (type 1), a *mechanical* CCSVI (type 2) and a mixed CCSVI of the previous two types (type 3). The method used to diagnose the presence of an obstacle due to external compression of the vessel (CCSVI type 2) and not by narrowing the inside of the same (CCSVI type 1) was a simple intuition: through the Valsalva maneuver and appropriate rotation of the head by the examined subject, it was possible to note a significant change in the crossing section area and the reappearance of the flow within the studied vessel. We have presented in 2011 at the National Congress of the Italian Society of Cardiology the division into 3 types of CCSVI.<sup>13,14</sup>

We focused three main parameters to stratify all studied patients for parametric and non-parametric statistical tests. First parameter was CCSVI-type; second parameter was ill duration; third parameter was expanded disability status scale (EDSS) total score.

In our sample the CCSVI-type-2 patients were few in number for statistical tests; so we analyzed only CCSVI-type-1 and CCSVI-type-3 patients. After the analysis of variance (ANOVA), we divided all ill duration into two groups (before and after the median value): less than 12 years (1-11 years of illness) and more than 11 years (12 or more).

EDSS total scores were analyzed as natural values (see Kurtzke,<sup>15</sup> for details) or as grouped values. We stratified EDSS total scores into three categories: *123* or *mild impairment* (EDSS total score: 1 or 2 or 3); *456* or *medium impairment* (EDSS total score: 4 or 5 or 6); *789* or *severe impairment* (EDSS total score: 7 or 8 or 9).

In our tests, we considered only *mild* (123) and *severe* (789) grouped EDSS values. Medium status of illness (456 grouped EDSS values) was not considered to increase strength in differences between initial and final MS period.

### Diagnosis of chronic cerebro-spinal venous insufficiency by echo-color-Doppler

In order to make a diagnosis of CCSVI, according to Zamboni's protocol, it is necessary that the patient has at least 2 of the following 5 parameters: i) reflux in internal jugular veins and/or vertebral veins in the supine and sitting position; reflux disease is defined as a reverse flow that lasts more than 0.88 seconds;<sup>16</sup> ii) reflux in intracranial veins (internal cerebral vein, basal vein of Rosenthal, and great cerebral vein of Galen); iii) presence of stenosis in the internal jugular vein using B-mode high-resolution echography; in this regard it is possible to identify hemodynamically (intraluminal defects such as fixed valves and/or malformed valves, spider webs, septa) or hemodynamically presence of stenosis in

the internal jugular vein B-mode high-resolution in this regard it is possible to identify stenosis hemodynamically (intraluminal defects such as fixed valves and/or malformed, spider webs, septa) or not-hemodynamically significant stenosis;<sup>17</sup> iv) no detectable flow using Doppler in the internal jugular veins and/or vertebral veins; v) reverse postural control of the main cerebral venous outflow pathways by evaluating the  $\Delta$  cross sectional area ( $\Delta$ CSA) in the internal jugular vein, that is the difference between the circumference of the internal jugular vein in the supine and sitting position, measured at its midpoint,<sup>18-22</sup> The finding of a negative CSA indicates a loss of postural control of the predominant way of venous drainage in the supine position.

During the ECD assessment before the patient is positioned in the supine position and then in a sitting position; the examination is conducted with both quiet breathing (without moving shoulders, to activate the respiratory pump and check if there is an induction of cerebro-spinal drainage) and deep breathing (to induce the maximum flow in the vessels which must be examined and for assessing the correct drainage and valvular functioning). In all our ECD assessments we performed the following ECD dynamic tests: neck movements, on right, on left rotation and anterior/posterior intrusion of the neck; 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.

The protocol requires the use of two probes: a 6.6-10 MHz linear probe, which is necessary for scanning the veins of the neck and a transcranial probe from 2.0 to 3.3 MHz for the study of the intracranial circulation. It can optionally be used a micro-convex probe from 5.0 to 8.0 MHz that allows to make a more accurate assessment of the lower part of the neck vessels, *i.e.* jugular-subclavian ostium and intracranial veins.<sup>7</sup>

### Statistical analysis

All data were analyzed by SPSS software to perform a stratified data description for numeric parametric variables. Statistical significance *between* and *within* groups was calculated on continuous variables by ANOVA to test the equality of means. The Chi-square ( $\chi^2$ ) Yates corrected test was used for non-continuous variables by Statcalc and Analysis programs from Epi-Info (2008, NIH & CDC Atlanta, GA, USA; Italian version 3.5.1).

A p value less than 0.05 was considered significant, and 95% confidence intervals were also calculated. The collected data of this study were assessed by the Kruskal-Wallis statistical test that is the non-parametric equivalent test of the analysis of variance in which the data are replaced by their rank; it was used because

the studied population did not follow a normal Gaussian distribution. This non-parametric method has the purpose of comparing the equality of medians in the different groups.

## Results

In Table 1 we show the cross tabulation between EDSS grouped values *vs* MS duration (less or more than 11 years) in CCSVI-type-1 and CCSVI-type-3 patients. The differences were statistical significant ( $P < 0.001$ ).

In Table 2 we show the ANOVA of EDSS values stratified by MS duration in CCSVI-type-1 and CCSVI-type-3 patients. The differences were statistical significant by Kruskal-Wallis test:  $H = 8.0345$ ; degree of freedom = 1 for CCSVI-type-1 ( $P < 0.01$ ); and  $H = 8.4757$ ; degree of freedom = 1 for CCSVI-type-3 ( $P < 0.01$ ).

In Table 3 we show the ANOVA of MS duration values stratified by EDSS grouped values in CCSVI-type-1 and CCSVI-type-3 patients. The differences were statistical significant by Kruskal-Wallis test:  $H = 44.2829$ ; degree of freedom = 1 for CCSVI-type-1 ( $P < 0.001$ ); and  $H = 37.3036$ ; degree of freedom = 1 for CCSVI-type-3 ( $P < 0.001$ ).

In Table 4 we show the ANOVA of EDSS values stratified by CCSVI-type-1 or CCSVI-type-3 patients in MS duration values (less or more than 11 years). The differences relived were not statistical significant.

If we consider instead the EDSS profiles of three clinical types we find that the relapsing-remitting (RR) patients are more present in the period before 11 years, the secondary progressive (SP) are more frequent after 11 years and the primary progressive (PP) uniformly distributed in the pre-and post-11 years.

## Discussion

The present study confirmed the data on the prevalence of CCSVI in MS patients, already mentioned in previous papers. In a large study, which involved 6 centers, Bastianello *et al.* analyzed the clinical data of 710 MS patients who underwent venous echo-color-Doppler. Significant associations were found between CCSVI and clinical data.<sup>23</sup> Similar results were quite recently described by an active multicenter epidemiological registry.<sup>24</sup> Therefore, our results replicate those coming from developed international scientific literature about this topic, as well as from several confirming meta-analysis.<sup>25</sup> Recently it was also shown that diagnostic procedure by ECD is reproducible between different operators from the technical perspective.<sup>26</sup> In recent years several studies have dealt with the association between CCSVI

**Table 1. Cutoff in chronic cerebro-spinal venous insufficiency-type-1 and -type-3 patients.**

EDSS	MS duration (years)				Total	
	Type-1		Type-3		Type-1	Type-3
Grouped values	<12	>11	<12	>11		
123	73	22	40	28	95	68
Row %	76.8	23.2	58.8	41.2	100.0	100.0
% Column	82.0	34.9	75.5	32.6	62.5	48.9
789	16	41	13	58	57	71
Row %	28.1	71.9	18.3	81.7	100.0	100.0
% Column	18.0	65.1	24.5	67.4	37.5	51.1
Total	89	63	53	86	152	139
Row %	58.6	41.4	38.1	61.9	100.0	100.0
% Column	100.0	100.0	100.0	100.0	100.0	100.0

P&lt;0.001

P&lt;0.001

EDSS, expanded disability status scale; MS, multiple sclerosis.

**Table 2. Expanded disability status scale values in cerebro-spinal venous insufficiency-type-1 and -type-3 patients.**

MS duration (years)	Obs		Σ		Mean		Variance		Std.Dev.			
	Type-1*	Type-3°	Type-1*	Type-3°	Type-1*	Type-3°	Type-1*	Type-3°	Type-1*	Type-3°		
<12	16	15	630.000	735.000	39.375	49.000	62.625	64.000	25.025	25.298		
>11	26	25	1600.000	1705.000	61.538	68.200	43.954	24.767	20.965	15.737		
	Minimum		25%		Median		75%		Maximum		Mode	
	Type-1*	Type-3°	Type-1*	Type-3°	Type-1*	Type-3°	Type-1*	Type-3°	Type-1*	Type-3°	Type-1*	Type-3°
<12	15.000	15.000	15.000	25.000	25.000	65.000	65.000	65.000	75.000	85.000	15.000	65.000
>11	15.000	15.000	65.000	65.000	65.000	75.000	75.000	75.000	85.000	85.000	65.000	75.000

MS, multiple sclerosis; Obs, number of observations; Σ, total sum; Std.Dev., standard deviation. \*Stratification by MS duration. Kruskal-Wallis: H=8.0345; degree of freedom (df)=1; P&lt;0.01; °stratification by MS duration. Kruskal-Wallis: H=8.4757; df=1; P&lt;0.01.

**Table 3. Multiple sclerosis duration values in cerebro-spinal venous insufficiency-type-1 and -type-3 patients.**

EDSS grouped values	Obs		Σ		Mean		Variance		Std.Dev.			
	Type-1*	Type-3°	Type-1*	Type-3°	Type-1*	Type-3°	Type-1*	Type-3°	Type-1*	Type-3°		
123	95	68	742.0000	733.0000	7.8105	10.7794	44.0701	58.2640	6.6385	7.6331		
789	57	71	990.0000	1480.0000	17.3684	20.8451	84.1654	87.8471	9.1742	9.3727		
	Minimum		25%		Median		75%		Maximum		Mode	
	Type-1*	Type-3°	Type-1*	Type-3°	Type-1*	Type-3°	Type-1*	Type-3°	Type-1*	Type-3°	Type-1*	Type-3°
123	0.0000	0.0000	2.0000	4.5000	6.0000	9.0000	11.0000	16.0000	27.0000	36.0000	2.0000	2.0000
789	3.0000	5.0000	11.0000	14.0000	16.0000	21.0000	22.0000	28.0000	46.0000	50.0000	11.0000	31.0000

EDSS, expanded disability status scale; Obs, number of observations; Σ, total sum; Std.Dev., standard deviation. \*Stratification by EDSS grouped values. Kruskal-Wallis: H=44.2829; degree of freedom (df)=1; P&lt;0.001; °stratification by EDSS grouped values. Kruskal-Wallis: H=37.3036; df=1; P&lt;0.001.

**Table 4. Expanded disability status scale values in patients with multiple sclerosis duration <12 and >11 years.**

CCSVI type	Obs		Σ		Mean		Variance		Std.Dev.			
	<12 years*	>11 years°										
1	16	26	63.0000	160.0000	3.9375	6.1538	6.2625	4.3954	2.5025	2.0965		
3	15	25	73.5000	170.5000	4.9000	6.8200	6.4000	2.4767	2.5298	1.5737		
	Minimum		25%		Median		75%		Maximum		Mode	
	<12 years*	>11 years°										
1	1.5000	1.5000	1.5000	6.5000	2.5000	6.5000	6.5000	7.5000	7.5000	8.5000	1.5000	6.5000
3	1.5000	1.5000	2.5000	6.5000	6.5000	7.5000	6.5000	7.5000	8.5000	8.5000	6.5000	7.5000

CCSVI, chronic cerebro-spinal venous insufficiency; Obs, number of observations; Σ, total sum; Std.Dev., standard deviation. \*Stratification by CCSVI-type. Kruskal-Wallis: H=1.2725; degree of freedom (df)=1; not significant; °stratification by CCSVI-type. Kruskal-Wallis: H=2.5481; df=1; not significant.

and MS. Among these, very interesting is the work conducted by Zivadinov and co-workers, who described the effective association between the neurodegenerative disease (MS) and this functional-hemodynamic finding which affects the vessels draining the cerebral blood. Furthermore they have shown that the higher disability the higher the prevalence of CCSVI is in MS patients. In particular, it emerged that the prevalence of CCSVI was higher in patients with progressive MS than in those with non-progressive MS. Therefore the authors concluded with the assumption that a high probability of disease progression which was associated with a high level of clinical disability was induced by morphological and hemodynamic alterations of cerebral veins.<sup>27</sup> In our previous study we have also found that patients aged more than 30 years showed a statistically significant higher presence of disabilities (mean EDSS score equal to 5) compared to younger patients (mean EDSS score equal to 3).<sup>28</sup> The same considerations may be made in present study, in which we highlighted that MS clinical severity worsening in CCSVI patients after 11 years of disease duration ( $P < 0.001$ ).

On 2009 Zamboni suggested that the RR and SP clinical courses are associated with significantly different CCSVI patterns compared to those with PP form.<sup>7</sup>

In the same paper, Zamboni suggest that location of venous obstructions could play a key role in determining the clinical course of the disease. Yamout *et al.*, however, have subsequently stated that the extra-cranial venous stenosis are unlikely the cause of MS, since in their study they were not present in most patients in the early stages of the disease and rarely involved more than one extra-cranial vein. They supposed, therefore, that CCSVI was a late secondary phenomenon.<sup>29</sup> Several authors have contrasted the initial hypothesis of Zamboni, for example Baracchini *et al.*, in their work, have shown that CCSVI is not a late secondary phenomenon of MS and is not associated with the worsening of disability.<sup>30</sup> Baracchini himself, in 2011, did not support a cause-effect relationship between CCSVI and MS onset.<sup>31</sup> Centonze *et al.* in their work also found no statistically significant differences in the frequency of CCSVI in MS patients and controls.<sup>32</sup> In addition, they have found no difference between patients CCSVI-positive and CCSVI-negative in terms of relevant clinical changes, such as the disease duration, the time that elapses between the onset and the first exacerbation, remitting or gradual course of disease and the risk of secondary progressive course. Another datum emerged from this study: there were no statistically significant differences between CCSVI-positive and CCSVI-negative MS patients in mean EDSS, mean index of progression and mean score of

severity of MS. No significant correlation was found between the severity of the disability and the number of positive criteria for CCSVI. Their results therefore indicated that CCSVI has no role in either the risk or severity of MS.

In present work, we do not found statistical significant differences between the different types of CCSVI and the EDSS score in patients with the same MS duration. Patients with progressive MS had higher probability of having also CCSVI than those with RR MS.

These findings suggested that the presence of CCSVI may favor a late development of MS in patients with a lower susceptibility to autoimmune diseases and may increase its severity. Already, other studies have found scores of clinical severity generally higher in CCSVI-positive patients.<sup>33</sup> Recently, some papers stated that CCSVI has no effect on neurological function and on the progression of disability in patients with MS.<sup>34</sup> Other case-control clinical works<sup>35</sup> showed that CCSVI was more frequent among MS patients with an ill duration more than 144 months. The same clinical aspects were found in SP MS and PP MS *versus* RR MS patients. A stronger association was found considering the forms SP and PP of MS. The authors therefore showed a higher frequency of CCSVI in MS patients, more evident in patients with advanced disease, suggesting that CCSVI may be related to disability in MS. Still about the study of the association between CCSVI and clinical disability in MS, Leone *et al.*<sup>36</sup> evaluated the association of CCSVI with MS in a cross-sectional blinded study and sought some association of CCSVI with the prevalence of MS. The prevalence of CCSVI was related to age in MS patients but not in controls. CCSVI-positive and CCSVI-negative patients were similar in clinical type, age at onset of illness, disability and fatigue. The disease duration was greater in CCSVI-positive patients than in negative ones. The authors concluded that CCSVI was not associated with MS, nor its severity. In addition, they could not affirm that CCSVI is a consequence of MS or aging. From this examination of the literature we understand how there are different and conflicting opinions about the correlation between CCSVI and MS, especially with regard to its relationship with the age from first clinical evidence, the degree of ill progression and patient capabilities deterioration.

## Conclusions

Present study confirmed and complete previous papers about relation between CCSVI and MS. On the same time, we found a strong correlation between MS illness duration and severity of EDSS score. In fact there is a clinical

severity cut-off after 11 years of illness in MS patients with CCSVI-type-1 or CCSVI-type-3. On the contrary, we did not found statistical significant differences comparing MS patients with CCSVI-type-1 *versus* MS patients with CCSVI-type-3. If we consider instead the EDSS profiles of three clinical types we find that the RR patients are more present in the period before 11 years, the SP are more frequent after 11 years and the PP uniformly distributed in the pre-and post-11 years. These data may suggest chronic vascular disease influence on MS. Further searches need in order to learn more about this new aspect in MS etiology.

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