Venous compression syndrome of internal jugular veins prevalence in patients with multiple sclerosis and chronic cerebro-spinal venous insufficiency

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Sandro Mandolesi*, Tarcisio Niglio°°, Augusto Orsini°°°, Simone De Sio***, Alessandro d'Alessandro°, Dimitri Mandolesi°, Francesco Fedele*, Aldo d'Alessandro**/°°°°

**Department Cardio-vascular and Respiratory Science, "Sapienza" University, Rome, Italy*
***Department of Medical Sciences, Oral and Biotecnology "G. d'Annunzio" University, Chieti, Italy*
****SAIMAL Dept. U.O. Occupational Medicine "Sapienza" University, Rome, Italy*
°Faculty of Medicine University of Foggia, Italy
°°Istituto Superiore di Sanità, Rome, Italy
°°°Department Vascular Surgery Gioia Hospital, Sora (FR), Italy
°°°°Department of Angiology "T. Masselli-Mascia" Hospital, San Severo (FG), Italy

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OBJECTIVES: *Analysis of the incidence of Venous Compression Syndrome (VCS) with full block of the flow of the internal jugular veins (IJVs) in patients with Multiple Sclerosis and Chronic cerebro-spinal venous insufficiency.*
METHODS: *We included 769 patients with MS and CCSVI (299 males, 470 females) and 210 controls without ms and ccsvi (92 males, 118 females). each subject was investigated by echo-color-doppler (ecd). morphological and hemodynamic ecd data were recorded by a computerized mem-net maps of epidemiological national observatory* on ccsvi and they were analyzed by mem-net clinical analysis programs.
RESULTS: *VCS of IJVs occurs in 240 subjects affected by CCSVI and MS (31% of total) and in 12 controls (6% of total). The differences between the two groups are statistical significant ($X^2 = 36.64$, $p<0.0001$).*
CONCLUSION: *Up to day there are no longitudinal studies that allow us to identify the WC of jugular and/or vertebral veins as etiology of a chronic neurodegenerative disease, but we note that Venous Compression Syndrome of IJVs is strongly associated with MS and CCSVI.*

KEY WORDS: Chronic Cerebro-Spinal Venous Insufficiency, Multiple Sclerosis, Venous Compression Syndrome

Introduction

Multiple Sclerosis (MS) is an inflammatory demyelinating disease that affects the central and peripheral nervous system. It's known that is an immune- mediated disorder caused by a complex interaction between genetics subset of the individual and not yet identified environmental factors [1].

The name *multiple sclerosis* refers to scars (sclerae—also known as plaques), in white matter of the brain and spinal chord [2].

MS plaques were described as venocentric since 1868 by Jean-Martin Charcot [3-5]. Moreover the cerebral vein wall in multiple sclerosis is subject to chronic inflammatory damage and it contains abnormally high levels of redox-active metals, particularly iron [6-9].

In 2008 Paolo Zamboni noted that MS is related to altered vascularization: the cervical and thoracic veins are not able to efficiently remove blood from the central nervous system (CNS) and it is presumably due to mul-

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Correspondence to: Mandolesi Sandro, via Montebello 17, 00185 Roma, Italy (e-mail: s.mandolesi@email.it)

tiple stenosis and malformations of principal extra-cranial outflow pathways of the cerebrospinal venous system. The internal jugular veins (IJVs) and the azygos vein (AZY) result more involved in the insufficiency.
This new nosological vascular pattern is defined Chronic Cerebrospinal Venous Insufficiency (CCSVI) and it results strongly associated with MS [10-12].
The hampered venous outflow is cause of hypoperfusion of brain parenchyma and it may contribute to MS pathology by causing chronic ischemia of the brain or iron toxicity [13].
Zamboni suggested five Echo-Color-Doppler (ECD) venous criteria that characterize this syndrome. The presence of two of them is enough to diagnose CCSVI.
- ***criterion 1***: constantly reflux or bidirectional present in an outflow pathway in supine and up-right;
- ***criterion 2***: reflux propagated upward to the deep cerebral veins, including internal cerebral vein, basal vein, Galen vein;
-***criterion 3***: evidence of IJVs anatomical stenosis or presence of anomalies and block, reflux constantly or bidirectional in the other;
-***criterion 4***: flow no detectable in the IJVs and VVs in clino and upright or in one position and presence of anomalies and reflux constantly or bidirectional in the other;
-***criterion 5***: negative difference in cross sectional area of the IJV (CSA) assessed in supine and standing posture (0° and 90°) in the IJV (CSA)[10,11].

The causes of the hampered venous outflow may be different and they can be classified in intraluminal obstacles (as valvoular malformations, septs etc.), parietal stenosis (segmental hypoplasiae, twisting, agenesia etc.) and ab-extrinseco compressions (bone compressions, muscolar entrapment etc.) [14,15].
Internal jugulars and vertebral veins, for their anatomic position, are exposed to a mechanic compression and this condition is well detectable by EDC.
Venous Compression Syndrome VCS in cerebral venous system is multifactorial. In fact there are at least three systems involved in its genesis. The bone apparatus (cervical vertebrae), the muscular apparatus (sternocleidomastoid, omo-hyoid, sternothyroid and scalene), the fascial apparatus (superficial, medium and deep band) [16,17].
If the IJV is not visible with ultrasound it can be explained by one of the following conditions:
1 atresia (congenital absence of the vessel);
2 hypoplasia (small congenital vessel);
3 post- thrombotic syndrome with no recanalization of the vessel;
4 venous compression syndrome (VCS).
To diagnose the VCS of the internal jugular vein simply make the subject rotate the head in order to see if the vessel expand. If this maneuver is ineffective we resort to the Valsalva maneuver. It allow to diagnose VCS and make a differential diagnosis [18].

By Echo Color Doppler (ECD), we defined: "Physiological internal jugular vein flow" (N) the cross area more than 6.0 mm^2 without blood block or reflux. "White compression" (WC) the internal jugular vein flow block by fully compression. "Black compression" (BC) the internal jugular vein flow reduction (cross area less than 6.0 mm^2) by severe compression. "White-Black compression" (WBC) the intermittent internal jugular vein flow, only during deglutition or postural maneuvers.
We found that White compression of IJV is equally distributed to lower levels (J1), medium (J2) and top (J3) of the vein and affects 48% of patients with CCSVI and MS[19]. The limit of the previous study was to be not performed as a case-control one. Hence the aim of this new our study is making an analysis of the prevalence of full block flow of IJVs in patients with CCSVI and MS compared to the prevalence of the phenomenon in a healthy group.

Methods

We investigated from 2010 by Echo-Color-Doppler (ECD) 769 patients with MS and CCSVI (299 males, 470 females) and 210 subjects without MS and CCSVI (92 males, 118 females). We assessed by ECD only the white compression at J2 level in supine and upright position. Control subjects were recruited among those addressed to undergo to vascular evaluation for chronic venous insufficiency of lower limbs.

Diagnostic evaluation of the cerebro-spinal venous drainage using ultrasound

The patients underwent a non-invasive study of cerebral venous return by the use of a combined trans-cranial and extra-cranial ECD. Those methods provide valid measures of venous hemodynamic (VH) parameters enabling an assessment of CCSVI cerebral venous return. The subjects were investigated in clinostatism and upright position (0° and 90°) in consideration of the postural effect on the main route of cerebral outflow[20]. Diagnosis of CCSVI was made in accordance to the Zamboni's criteria [21].
In order to complete the evaluation of the cerebro-spinal venous drainage we investigated about the presence of the venous compression syndrome of IJVs and/or VV.
We define VCS when a normal vein not visible with ultrasound, because collapsed, may expand with neck position changes and/or Valsalva [22]. 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.

Compressions can be detected through the head in the front and/or right and/or left lateral position. These types of compression can be find at different level of IJVs (J1, J2 and J3) or at V2 and V3 level of VVs when the veins are not visible by ECD.
Morphological and hemodynamic ECD data were recorded by a computerized MEM-net maps, and they were analyzed by MEM-net Clinical Analysis programs (Table I).
The MEM map 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 before mentioned hemodynamic conditions and also venous anomalies.
All database were treated in respect with the Italian Privacy Laws and they are available on the National Epidemiological Observatory on CCSVI (websites: http://www.osservatorioccsvi.org/ and http://www.mem-net.it/) [23,24].

Statistical analysis

All data were Analyzed by programs from EPI-INFO [13] to perform a stratified data description for parametric numeric variables. Statistical significance "between" and "within" groups on continuous variables was Calculated by the analysis of variance (ANOVA) to test the equality of means. The Chi-square (χ^2) Yates corrected test was used for non-continuous variables by StatCalc and Analysis (EPI-INFO). A p value <0.05 was significant Considered.

Results

Patients with right or left frontal white compressions stratified by sex are not statistically significant in female vs male and right vs left compressions (Table I).
In the same sample the patient's position is statistically significant in test supine vs upright (p<0,001) (Table II).

Table I - *Shows patients with right or left frontal white compressions stratified by sex. The revealed differences are not statistically significant in female vs male and right vs left compressions.*

			J2 Frontal White Compression	
	Patients	**Sex**	**With WC**	**without WC**
CCSVI	769	**F+M**	240	529
+SM	470	**F**	198	272
	299	**M**	42	257
NO CCSVI	210	**F+M**	12	198
NO SM	118	**F**	9	109
	92	**M**	3	89

Table II - *Shows that during ECD execution the patient's position is statistically significant in test supine vs upright (p<0,001).*

Patients	**Sex**	**SUPINE**	**UP-RIGHT**
111	F+M	40	90
64	F	16	57
47	M	24	33
99	F+M	34	85
54	F	16	48
45	**M**	18	37
210	**F+M**	74	175

Table III - *Shows that VCS occurs in 240 subjects affected by CCSVI and MS (31% of total) and in 12 controls (6% of total). The differences between the two groups are statistical significant (X^2 = 36.64, p<0.0001).*

		Prevalence of J2 frontal white compression	
	Pazienti	**Con Wc**	**Senza Wc**
CCSVI +SM	769	240 (31%)	529 (69%)
NO CCSVI NO SM	210	12 (6%)	198 (94%)

Venous Compression Syndrome of J2 occurs in 240 subjects affected by CCSVI and MS (31% of total) and in 12 controls (6% of total). The differences between the two groups are statistical significant (χ^2 = 36.64, p<0.0001) (Table III).

Discussion

Since 1960 physicians has studied the possible relationship between working posture position and alterations of venous drainage [25-26]. The presence of CCSVI in our patients with MS confirms the data in the literature about the correlation between altered cervical venous flow and this neurologic disease[2 7-28].
ECD of the jugular veins of the neck allowed recognizing three different altered cervical hemodynamic conditions of CCSVI the Type 1, Type 2 and Type 3. Type 1 with intra venous block, Type2 with extra venous compression, Type 3 with both intra and extra conditions This classification could be used to customize in future the therapeutic strategy based on the patient's vascular condition.
The study confirmed that the higher severity of the MS corresponds to a longer duration of the disease.

This evidence is in agreement with another study conducted by our research group. We compared two groups of patients with MS: the first with <30 years (group 1) and the second one with > 30 years (group 2). We have shown that in the second group patients had a higher percentage of blocked flow in cervical veins and greater severity in the EDSS, in relation to their longer disease duration [29]. Comparing the misalignment in the cervical vertebrae, the anterior intrusion between the first two vertebral bodies is greater than two-fold in patients with MS rather than in patients without neurologic disease. Recently it has been documented, in two patients with MS, a compression syndrome of IJV as consequence of aberrant omohyoid muscle. The muscular resection restored IJV flow supporting the hypothesis that muscular compression may be responsible of venous angioplasty inefficacy [16]. Other muscles can be involved in such venous compression: for example, the scalene muscle could entrap the J1 terminal segment of the internal jugular vein, while the sterno-mastoid muscle can compress the J3 segment of the internal jugular vein. We suppose that all these compressions may be caused by the misalignment of cervical vertebrae with stretching of the muscles and aponeurosis with effect on neck veins. This intermittent compression block of vertebral and jugular veins could be one of the multi-factorial causes of the worst clinical conditions in MS patients with CCSVI. These patients frequently had head and neck trauma. There is a proposed relationship between MS and upper cervical subluxation. Elster conducted a study on upper cervical subluxation and it's connection to MS and Parkinson's disease [30]. These data, absolutely innovative in scientific literature, confirmed that the structure of cervical spine may altered flow neck of these patients. In addition, the clinical classification of CCSVI about the etio-pathogenesis of altered cervical flow can be a real novelty in the therapeutic approach to MS. Chai did a study on the effects of unilateral jugular compressions in pigs which show an cerebral blood flow increase in both hemispheres [31]. Tovedal highlighted in pigs a progressive obstruction of the superior venae cavae leads to measurable signs of impaired cerebral perfusion [32]. Frydrychowsky confirmed the same data in humans in a study in which they closed both jugulars for three minutes [33] looking at how an acute bilateral jugular congestion leading to an hyperkinetic increase of cerebral circulation with pial arteries pulsation due to the reduction of Windkessel effect. To contrast the high resistance of the venous drainage the pial arteries try to expand but, due to the sub arachnoid space inextensibility, follow an increase of intracranial pressure[34].

There are many paper on the possible outcomes of a block flow of the internal jugulars and chronic brain diseases, as in multiple sclerosis. In future, will be better investigated if a block flow of one jugular vein or bilateral block flow due to postural position could affect the brain drainage so to create a chronic injury.

Conclusion

The authors suggest that the external myofascial compressions or misalignment of the first cervical vertebrae, induced by head movements or posture changes may have a role in the reduction of Windkessel effect by blocking the venous brain drainage in subjects with VCS White of the jugular veins. This condition is able to increase the pulse energy of pial arteries and could create a potential injury in brain microcirculation. Up to day there are no longitudinal studies that allow us to identify the WC of jugular and/or vertebral veins as etiology of a chronic neurodegenerative disease, but we note that Venous Compression Syndrome of IJVs is strongly associated with MS and CCSVI.

Riassunto

Obbiettivo: Analisi della prevalenza della Sindrome Compressiva Venosa (VCS) con blocco completo del flusso delle vene giugulari interne (IJVs) nei pazienti con sclerosi multipla e insufficienza venosa cronica cerebrospinale.

Metodo: Sono stati inclusi 769 pazienti con sclerosi multipla e CCSVI (299 maschi, 470 femmine) e 210 controlli senza SM e CCSVI (92 maschi, 118 femmine). Ogni soggetto è stato indagato con Echo-Color-Doppler (ECD). I dati ECD morfologici ed emodinamici sono stati registrati sulla mappa informatizzata MEM-net dell'Osservatorio Nazionale Epidemiologico della CCSVI che utilizza programmi di analisi cliniche ed emodinamiche.

Risultati: La VCS delle IJVs si è riscontrata in 240 soggetti affetti da CCSVI e SM (31% del totale) e in 12 controlli (6% del totale). Le differenze tra i due gruppi sono statisticamente significativa (χ^2 = 36.64, p <0,0001).

Conclusione: Sino ad oggi non ci sono studi longitudinali che ci permettono identificare la VCS delle giugulari e / o delle vene vertebrali quale eziologia di una malattia neurodegenerativa cronica, ma si nota che la sindrome di compressione venosa delle IJVs è fortemente associata alla SM e alla CCSVI.

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