Jugular diameter and venous reflux

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OBJECTIVES: *Aims of this study were to investigate the prevalence of reflux on internal jugular veins(IJV) by Valsalva maneuver and to define the association between reflux of IJV in subjects with both CCSVI and MS.*
METHODS: *We recruited 393 patients with MS and CCSVI. Study participants underwent EchoColor Doppler exam in order to define IJV diameter at confluence in subclavian (JSd). Subjects were divided in three groups: group "1<JSd<6 mm" (subjects with jugular diameter less than 6mm); group "6≤JSd<10 mm" (subjects with jugular diameter equal or more than 6 but less than 10); and group "JSd≥10 mm" (subjects with jugular diameter equal or more than 10 mm).*
RESULTS: *In our sample the Jugular mean diameter was 8 ± 2 mm. There were not significant differences in mean diameter values in left/right jugular, after grouping jugular diameters into three groups by mean sample values ± standard deviation. Veins ≥10mm were more observed than veins ≤6 mm. Significant difference were found in male vs female prevalence of subject included in "JSd≥10 mm" (30.7% vs 16.7%. X2 =22.9622 with df=2 p<0.0001). Regarding the group "JSd≥10 mm", while in males the Valsalva+/Valsalva- ratio was about 1:3, in females the ratio was about 1:2. Female are more aged in "JSd≥10 mm" group vs female subjects in "1<JSd<6 mm" or "6≤JSd<10 mm" groups (p<0.05: Kruskal-Wallis H test = 8,0832 with df=2). Aged females have Jugular diameter larger than younger females.*
CONCLUSION: *By the analysis of the data, we may suppose that the females with both CCSVI and MS may present a wall Miopragia because there are significant differences in Valsalva+/ Valsalva– Ratio in females vs males subjects included in "JSd≥10 mm" group (about 1:2 vs. 1:3).r Moreover jugular dilatations are equally present in left and right side and it can confirm the wall Miopragia hypothesis. The prevalence of V+ maneuver grows with the IJV diameter, therefore we presume that IJV dilatation is linked with the presence of jugular reflux. Further studies are required to consolidate our observations.*

KEY WORDS: CCSVI, Jugular vein diameter, Valsalva maneuver

Introduction

Multiple Sclerosis (MS) is an inflammatory demyelinating disease with autoimmune pathogenesis that affects the central and peripheral nervous system, causing a variety of signs and symptoms; clinical manifestation are mainly due to scars (better known as plaques or lesions) in the white matter of the brain and spinal cord. It is believed that MS is an immune-mediated disease caused by a complex interaction between genetics subset of the individual and not yet identified environmental factors[1]. 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 stenosis and malformations of jugular veins and azygos.

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Chronic cerebro-spinal venous insufficiency (CCSVI), as has been claimed by Zamboni et al., is a pathological condition characterized by hampered venous outflow from central nervous system and spinal cord due to stenosis or occlusion of extracranial veins, at level of the internal jugular veins (IJV), vertebral veins and/or azygous veins.

Abnormal venous outflow seems to be the cause of iron deposits around cerebral perivascular tissue. According to Zamboni, patients with MS undergone to echo color Doppler and/or venography of intracranial and neck vessels showed a high prevalence of CCSVI (about 71%) and new collateral circulation. By contrast, healthy controls showed a low prevalence of CCSVI(7.1%) [2].

These vascular lesions are frequently represented by segmental hypoplasia or intraluminal defects, generally classified as truncular venous malformations. These truncular lesions are the result of an arrest in the development that occurs in the late phase of the formation of vascular trunk during fetal life. An immature or incomplete development of the main venous axis during fetal life produces malformations such as aplasia, hypoplasia or hyperplasia of the vessels or it can cause the formation of abnormal vessels for the presence of intraluminal obstruction or aneurysmal dilatation [3,4]. The finding of an increased prevalence of abnormal venous drainage in patients with MS suggested that these vascular changes might be a contributing factor for the development and progression of the disease [5,6].

Zamboni et al. proposed five sonographic criteria of CCSVI; in order to make a diagnosis at least two of them must be satisfied [7].

A positive Valsalva maneuver shows that the terminal and pre terminal valvule of IGV are not competent. The reverse flow observed with ECD (echocolordoppler) is called "reflux of Jugular vein".

When a person forcefully expires against a closed glottis, changes occur in intrathoracic pressure that dramatically affect venous return, cardiac output, arterial pressure, and heart rate. This forced expiratory effort is called a Valsalva maneuver (VM). Similar changes occur when the thoracic and abdominal muscles are strongly contracted. This can occur when a person strains while having a bowel movement. Similar changes can also occur when a person lifts a heavy weight while holding their breath.

Valsalva maneuver is composed by four phases according to arterial blood pressure (ABP) changes [8-10].

With the beginning of the strain (phase I), there is a transient increase in ABP that is resulted from transmission of the intrathoracic pressure to the arterial system. At phase II, continuously increased intrathoracic pressure will prevent venous return from vena cave to the heart.

When the strain is relieved (phase III), more venous blood volume pools in the expanded intrathoracic capitance veins because of sudden decrease of intrathoracic pressure, which in turn, decreases left atrial filling and ABP. This is follow immediately by an overshoot in ABP (phase IV) when the atrial filling is normalized accompanied by remain elevated sympathetic tone (e.g. increased systemic vascular resistance). Cerebral blood flow (CBF) will change in response to the changes in cerebral perfusion pressure (CPP). There is a similar four-phase CBF changes during VM. Besides decreased ABP, VM will cause elevated CVP at phase II, which has effects on CPP and CBF during VM as well. Using transcranial Doppler (TCD), systemic ABP and flow velocities in middle cerebral arteries (MCA) during VM can be simultaneusly recorded.

The aim of this study was to assess, in supine position, by ECD: the correlation between the different groups of diameter of the confluence jugulo-subclavian and the positive Valsalva maneuver in patients with CCSVI and MS.

Methods

The study was performed on years 2011-2013 studying all "new" patient that asked a first visit. Out from these subjects, 393 patients were finally enrolled in accordance with inclusion/exclusion criteria (279 F plus 114 M; mean aged 42 years).

All clinical data were collected into an electronic database by MEM-net software.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/)[11,12].

Ultrasound evaluation of neck vessels by ECD

The study of the cerebro-spinal system was conducted using two probes: a 7.5 MHz linear transducer for scanning of neck veins and a micro-convex probe where the subclavian-jugular confluence was deeper. The echo-device used for the ECD was a My-lab Esaote Vinco.

Patients were studied on a bed with the head positioned ad 0°, in the supine position.

We collect all ECD of the internal jugular veins, on the Hemodynamic Morphological map MEM.net. (Fig. 1).

The internal jugular veins are divided into three segments. The proximal segments are J1, the medium segments are J2 and the distal are J3. J1 starts from the confluence into subclavian vein and arrives at the inferior level of thyroid (Fig. 2). J2 segment starts from inferior level of thyroid and arrive to the jugular point (that is when the vein crosses the bifurcation of carotid arteries); J3 segment goes from the jugular point to the higher point detectable by ECD.

To reduce the human error the internal jugular diameter measures were performed only in the J1 segment and by ECD sagittal scan where the section is the maximum. Patients had to be able to cooperate during the exam,

in fact, they were asked to perform Valsalva maneuver, making a push with the thorax keeping closed mouth and nose. This maneuver was performed to identify a reflux on IJV and to evaluate the continence of venous valves. Patients attempted Valsalva maneuver in clinostatic position. The evaluation of a positive or negative Valsalva maneuver was related to reverse flow detected by ECD assessment which starts from jugulo-subclavian confluence upward until at least J2 level. We considered reflux a reversal flow for a duration at least of 0.88 seconds from its physiological direction. Reverse flows have also been noted via inferior, middle, upper thyroid and facial veins in J3 level, but the presence of these ones were not considered in determining the positivity of a Valsalva maneuver. Instead, we only considered a retrograde flow from the confluence as positive; this reverse flow was caused by incontinence of terminals and preterminal valves of the IJV. We measured the diameter of the jugular-subclavian junction bilaterally, at supine position, during normal respiration this being the most suitable posture to fill most of the jugular veins.

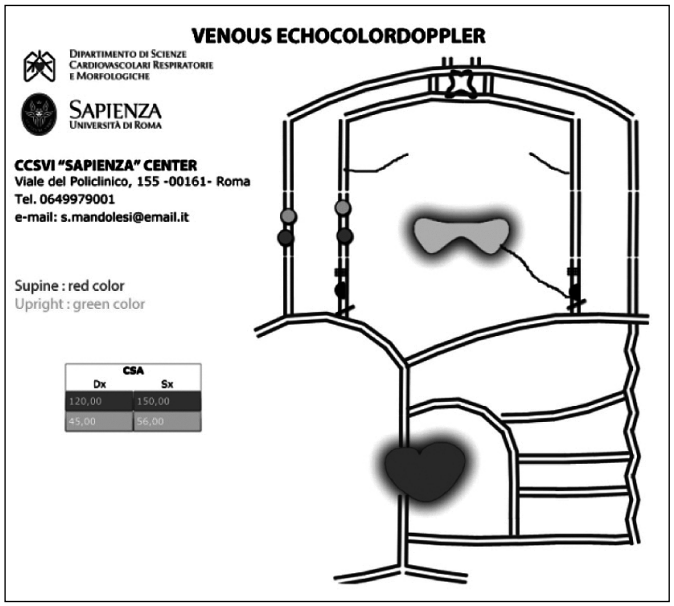

Fig. 1: Reporting a printing of an ECD examination with hemodinamics and morphological symbols.

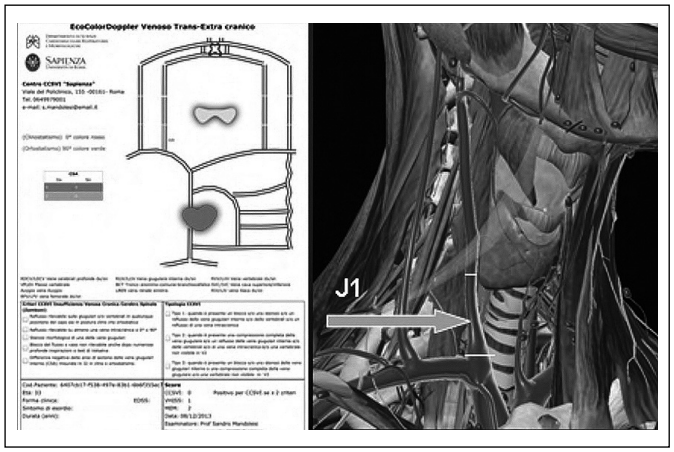

Fig. 2: Segment J1 of the right internal jugular vein.

Statistical Analysis

All data were analyzed by SPSS software 19th 2012 to perform a stratified data description for numeric parametric 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 (χ^2) Yates corrected test was used for non-continuous variables by Statcalc and Analysis programs from Epi-Info (2008, NIH & CDC Atlanta, USA; Italian version 3.5.1). A p value < 0.05 was considered statistically significant, and 95% confidence intervals were also calculated.

Results

Our sample study had a mean IJV diameter (JSd) of 8 ± 2 mm (Table I) and patients were divided into three groups (Table II):

– "**1<JSd<6 mm**" **group** = subjects with Jugular diameter less than 6.0 mm (value less than a mean sample value minus one standard deviation; $x < \mu - S.D. = x < 8 - 2 = x < 6$ mm);

– "**6≤JSd<10 mm**" **group** = subjects with Jugular diameter equal or more than 6.0 and less than 10 mm (value between mean sample value ± one standard deviation; $\mu - S.D. \geq x > \mu + S.D. = 8 - 2 \geq x > 8 + 2 = 6 \geq x > 10$ mm);

TABLE I - *All Jugulars' mean diameter (in mm)*

Obs.		Mean		Std.Dev.	
786		8,1038		2,1151	
Min	25%	Median	75%	Max	Mode
2,1000	6,6000	8,0000	9,5000	14,4000	7,6000

TABLE II - *Grouped Jugular diameters: Share of patients for each group*

Grouped Jugular diameters	Obs.	Percent
"1<JSd<6 mm"	120	15.3%
"6≤JSd<10 mm"	503	64.0%
"JSd≥10 mm"	163	20.7%
Total	786	100.0%

– **"JSd≥10 mm" group** = subjects with Jugular diameter equal or more than 10.0 mm (value equal or more than a mean sample value plus one standard deviation; $x \geq \mu + S.D. = x \geq 8 + 2 = x \geq 10$ mm).
There are not significant differences in mean diameter values in left/right jugular, also after grouping jugular diameters into three groups by mean sample values ± standard deviation.
There are significant differences in Female vs. Male subjects (F=16.7% vs. M=30.7% ≈ 1:2) included in "JSd≥10 mm" group ($p<0.0001$: $X^2 = 22.9622$ with df=2) (Table III).

TABLE III - *Grouped Jugular Diameters: Females vs Males*

Grouped Jugular diameters	Female	Male	Total
"1<JSd<6 mm"	98	22	120
Row %	81.7	18.3	100.0
% Column	17.6	9.6	15.3
"6≤JSd<10 mm"	367	136	503
Row %	73.0	27.0	100.0
% Column	65.8	59.6	64.0
"JSd≥10 mm"	93	70	163
Row%	57.1	42.9	100.0
% Column	16.7	30.7	20.7
Total	558	228	786
Row%	71.0	29.0	100.0
% Column	100.0	100.0	100.0

There are statistical significant differences in mean values (5.0 ± 0.8 vs 11.1 ± 0.9 mm) after grouping all patients into "1<JSd<6 mm" or "JSd≥10 mm" groups ($p<0.0001$: Kruskal-Wallis H test = 206,7874 with df=1) (Table IV). On the contrary, these data are not statistical significant in analysis female vs. male.
Female are more aged in "JSd≥10 mm" group vs female subjects in "1<JSd<6 mm" or "6≤JSd<10 mm" groups ($p<0.05$: Kruskal-Wallis H test = 8,0832 with df=2). Aged female have Jugular diameter more large than younger female (Table V). On the contrary, stratification in male mean age by grouped Jugular diameters are not statistical significant.

Discussion

Most of the cerebral venous drainage is via the extracranial venous pathway in the neck. Other extracranial venous outflow pathways, such as the emissary veins of the middle cranial fossa draining the superficial and the deep middle cerebral vein contribute to a lesser extent. The main cerebral venous outflow tract in the neck is represented by internal jugular vein (IJV), vertebral venous system, and the deep cervical veins (cervical soft tissue veins). These three venous pathways show multiple anastomoses between them in the neck, especially in the region of the cranio-cervical junction. Among them, IJV and the vertebral vein can be easily detected by color Duplex ultrasound [13,14].
IJV is the largest vein in the neck and is considered to be the most important cerebral venous outflow pathway.

TABLE IV - *Grouped Jugular diameters: values less than μ – S.D. vs. values more than μ + S.D.*

Grouped Jugular diameters	Obs.	Mean	Std.Dev.			
"1<JSd<6 mm"	120	5,0208	0,8052			
"JSd≥10 mm"	163	11,1656	0,9702			
Grouped Jugular diameters	**Minimum**	**25%**	**Median**	**75%**	**Maximum**	**Mode**
"1<JSd<6 mm"	2.1000	4.7500	5.2000	5.6500	5.9000	5.8000
"JSd≥10 mm"	10.0000	10.4000	11.0000	11.7000	14.4000	10.0000

TABLE V - *Female mean age grouped by Jugular diameter.*

Female (age)	Obs	Mean (age)	Std.Dev.			
"1<JSd<6 mm"	98	41.9592	12.0077			
"6≤JSd<10 mm"	367	41.8583	12.4756			
"JSd≥10 mm"	93	46.4301	13.2258			
Female (age)	**Minimum**	**25%**	**Median**	**75%**	**Maximum**	**Mode**
"1<JSd<6 mm"	18	33	42	50	67	48
"6≤JSd<10 mm"	14	33	410	49	90	33
"JSd≥10 mm"	20	35	44	57	75	33

TABLE VI - *Grouped Jugular diameters: Valsalva's maneuver negative vs. positive (p<0.01: X= 11.0678 with df=2).*

Grouped Jugular diameters	"1<JSd<6 mm"	"6≤JSd<10 mm"	"JSd≥10 mm"	Total
Valsalva negative	91	335	93	519
Row%	17.5	64.5	17.9	100.0
% Column	75.8	66.6	57.1	66.0
Valsalva positive	29	168	70	267
Row%	10.9	62.9	26.2	100.0
% Column	24.2	33.4	42.9	34.0
Total	120	503	163	786
Row%	15.3	64.0	20.7	100.0
% Column	100.0	100.0	100.0	100.0

TABLE VII - *Grouped Jugular diameters: Valsalva's maneuver negative vs. positive in Female subjects (p<0.01: X= 11.7323 with df=2) or in Male subjects (n.s.)*

	Grouped Jugular diameters in Female			
F pts	"1<JSd<6 mm"	"6≤JSd<10 mm"	"JSd≥10 mm"	Total
Valsalva negative	73	231	47	351
Row%	20.8	65.8	13.4	100.0
% Column	74.5	62.9	50.5	62.9
Valsalva positive	25	136	46	207
Row%	12.1	65.7	22.2	100.0
% Column	25.5	37.1	49.5	37.1
Total	98	367	93	558
Row%	17.6	65.8	16.7	100.0
% Column	100.0	100.0	100.0	100.0
	Grouped Jugular diameters in Male			
M pts	**"1<JSd<6 mm"**	**"6≤JSd<10 mm"**	**"JSd≥10 mm"**	**Total**
Valsalva negative	18	104	46	168
Row%	10.7	61.9	27.4	100.0
% Column	81.8	76.5	65.7	73.7
Valsalva positive	4	32	23.5	60
Row %	6.7	53.3	40.0	100.0
% Column	18.2	24	34.3	26.3
Total	22	136	70	228
Row %	9.6	59.6	30.7	100.0
% Column	100.0	100.0	100.0	100.0

Venous flow from the superficial and deep venous system is directed toward the sigmoid sinus via the transverse vein. The Sigmoid sinus drains into the IJV that joins with the subclavian vein to form the brachiocephalic vein. Brachiocephalic veins flow into superior vena cava (SVC), which ultimately drains venous blood into the heart.

The vertebral venous system consists of two components, one is the vertebral venous plexus and the other is the vertebral vein [15].

The vertebral venous plexus can be subdivided into the internal (posterior and anterior internal vertebral plexus) and the external (posterior and anterior external vertebral plexus) vertebral plexus. Complex connections of the cerebral venous outflow with the vertebral venous system over the cranio-cervical junction have been displayed in several human cadavers and angiographic studies. There are anastomosis between the anterior internal vertebral venous plexus, vertebral vein, and deep cervical veins. The pterygoid plexus and facial veins are other

important extracranial venous collateral pathways. Extracranial venous drainage is position dependent [15-17]. In the supine position, the IJV is the main route for cerebral venous drainage.

Venous return is modified by the pressure gradients of blood flow into the thorax. Inspiration augments venous return to the heart by the generation of negative intrathoracic pressure. On the contrary, breath-holding results in increased abdominal and thoracic pressure and consequently it cause a decrease in venous outflow via the cervical veins [18,19]. On duplex sonography of the extracranial arteries, the cervical veins were not routinely examined, because clinically relevant symptoms were not evident. In the past, duplex sonography has been used to diagnose pathologic conditions of the IJV, as the dural arterio-jugular venous fistula and jugular or central venous occlusions. Recently, several neurologic disorders have been found to be associated with abnormal flow patterns in the IJV, which were detected by duplex sonography [7].

The IJV valve (IJVV) is located about 0.5 cm above the union of the subclavian vein and the IJV at the lower limit of the jugular bulb. IJVVs are seen in 96.8% of the general population [20]. Usually the IJVV is bicuspid and it can be detected by high resolution ultrasonography [21,22]. The valve closes once during each cardiac cycle. The closure of the valve occurs during diastole when the atrium transmits backward pressure from the right atrium into the superior vena cava and then into the IJV. The valve is then open during mid-systole.

The IJVVS are the only venous valves between the heart and the brain and they serve an important role in preventing backflow of venous blood and backward venous pressure into the cerebral venous system during conditions of increased venous or intrathoracic pressure as coughing. Without a competent IJVV, a sustained or prolonged retrograde-transmitted venous pressure via the IJV might lead to cerebral venous hypertension or congestion. Internal jugular vein valve incompetence (IJVVI) it's defined if a repeated Valsalva manoeuvre (VM) led to a retrograde jugular flow assessed by extracranial duplex ultrasound.

Patients who have an elevated central venous pressure, due to congestive heart disease, tricuspid valve regurgitation, primary pulmonary hypertension, and chronic obstructive pulmonary diseases present an higher prevalence of IJVVI. These findings support the hypothesis that venous valve incompetence is acquired and linked to venous hypertension [23-25]. Cannulation and catheterization of the IJV may cause persistent incompetence of the IJV valve [26]. Prevalence of IJVVI is not clear, many studies were conducted over the last years and the reported prevalence of IJVVI ranges widely from 20-40% of normal individuals, depending on the imaging method and the study population [26,27]. Recently, several neurologic disorders have been found to be related to IJVVI. These disorders are transient global amnesia (TGA) [27,28], transient monocular blindness [29], cough headache [30] and primary exertional headache [31]. These associations suggest that cerebral venous hypertension or congestion might play a major role in the mechanism of these disorders.

In venous segments without venous valves (e.g. the distal IJV and intracerebral veins), just a reversed pressure gradient could produce venous reflux. In Jugular vein reflux (JVR), there is an abnormal (reversed) pressure gradient resulting from increased venous pressure proximally with an incompetent venous valve. JVR indicates an increased proximal venous pressure, which might impede cerebral venous outflow and might induce neurologic dysfunctions [6,27-31]. In physiologic situations, most frequently encountered reversed pressure gradients result from many Valsalva-like activities which increase intra-thoracic pressure. The VM is frequently encountered in many daily activities in which straining occurs. Lifting of heavy loads, defecation, playing of wind instruments, coughing, and vomiting are all activities that simulate the VM.

Long-term repeatedly increased pump back pressure by these Valsalva-like activities may damage the venous valves, leading to valve degeneration and their possible incompetence [27,34,35]. This explains the high frequency of IJVVI seen in the elderly. Moreover, if there is a persistent and high reversed pressure gradient, like in central venous obstructions, JVR will be continuous.

Continuous JVR has been mostly reported on the left side because of the anatomic characteristics of the left brachiocephalic vein (it run through the narrow space between the sternum and the thoracic outlet arteries before entering the SVC).

Other causes of central venous obstruction producing continuous JVR are mediastinal goiter, mediastinal masses, aortic aneurysm, venous thrombosis (SVC syndrome), and severe congestive heart failure[36-38].

MS is known to be associated with the HLA region on 6p21.32. Copy number variations (CNV) contained in the HLA locus region in patients with the novel phenotype of CCSVI/VM and MS were mapped in detail, demonstrating a significant correlation between the overall number of known CNVs found in the HLA region and the number of stenosing venous malformations identified in patients. Furthermore pathway analysis of the HLA region revealed common routes of interaction of several of the genes involved in angiogenesis and immunity contained within this region [39].

Several studies have shown that the internal jugular veins have a physiological change in diameter in relation to different factors. First of all the diameter of IJV varies in relation to the position of the body, according to the intra-thoracic pressure and in relation to the value of central venous pressure; a recent study has shown that the size of the IJV changes with the simple rotation of the head during the performance of ECD [19,40].

In the study of Mandolesi et al. has been shown that the block of the drainage by extrinsic compression in

116 patients supine and in 232 in the upright (48% of total). The passage from the supine to the upright position causes an increased incidence of compressions. The homo-lateral head rotation to the investigated IJV causes a significant increase of the extrinsic compressions [41].
Venous abnormalities have been associated with different neurological conditions, also with MS.
Besides the description of the association between extracranial venous malformations of the cerebral veins and neurodegenerative disorders, little is known about the jugular wall.
Coen was the first that detected an altered ratio of type I/III collagen in the IJVs of MS patients, without any differences in cellularity or connective tissue distribution [42]. This feature has been described in many other conditions (e.g., varicose saphenous veins, haemorrhoids, or also paraoesophageal hernia, pelvic organ prolapse), suggesting a possible role of connective alterations in MS pathogenesis [43-45].
In a post mortem study comparing MS patients with people who died for different reasons, valvular and other intraluminal abnormalities were identified in 72% of MS patients and in 17% of controls [46].
Zamboni found, using a scanning electron microscopy, intraluminal septa and/or defective valves blocking the flow in the distal internal jugular vein of seven patients were studied together with the adjacent wall and compared with control specimen [47].
Pascolo, performing sequential X-ray Fluorescence (XRF) analyses on large tissue areas at 12.74 keV, showed an increased Ca presence in the pathological samples of IJV, mainly localized in tunica adventitia microvessels. Investigations at lower energy demonstrated that the high Ca level corresponded to micro-calcifications, also containing P and Mg. Moreover histological examination demonstrated the presence of small basophilic bodies suggestive of micro-calcifications within the connective tissue of the tunica adventitia [48].
Farina used the histochemical data in order to explain the typical hourglass appearance of a part of the IJVs in MS patients and defined it as "miopragic" [49]. In his study explained that jugular collapse, secondary to extrinsic muscular compression, is the expression of a congenital weakness of vessel walls, likely because of a dysregulation of collagen synthesis.

Conclusions

Mean jugular diameter at confluence is 8 ± 2 mm.
As expected, males have bigger JSd than females: veins with JSd > 10 mm were more observed in males (M 30.7% vs F 16%;the ratio is about 2:1).
Several aspects lead us to suppose the presence of a wall miopragia in patients with both CCSVI and MS.
First of all there were not significant differences in mean diameter values in left/right jugular, after grouping jugular diameters into three groups by mean sample values ± standard deviation.
Moreover the prevalence of V+ maneuver grows with the IJV diameter therefore we presume that IJV dilatation is linked with the presence of jugular reflux.
This wall miopragia seems to be more common in females. In fact aged females have jugular diameter larger than younger females, on the contrary stratification in male mean age by grouped jugular diameters are not statistical significant.
Furthermore, regarding "JSd≥10 mm" group, while in males the V+/V- ratio was about 1:3 in females the ratio was about 1:2.
In conclusion by the analysis of the data we may suppose that patients with both CCSVI and MS, especially females, may present a wall miopragia.
Further studies are required to consolidate our observations.

Riassunto

OBIETTIVI: L'obiettivo di questo studio è di indagare la prevalenza di reflusso sulle vene giugulari interne (IJV) tramite la manovra di Valsalva e di definire l'associazione tra il reflusso sulle IJV in soggetti con CCSVI e SM.
METODI: Abbiamo reclutato 393 pazienti con SM e CCSVI. I partecipanti allo studio sono stati sottoposti a esame EcoColorDoppler per misurare il diametro della IJV alla confluenza in succlavia (JSd). I soggetti sono stati divisi in tre gruppi: gruppo "1 <JSd <6 mm" (soggetti con diametro giugulare inferiore a 6mm); gruppo "6≤JSd <10 mm" (soggetti con diametro giugulare pari o superiore a 6, ma inferiore a 10); e gruppo "JSd≥10 mm" (soggetti con diametro uguale o maggiore di 10 mm).
RISULTATI: Nel nostro campione diametro medio delle giugulari alla confluenza in succlavia è stato di 8 ± 2 mm. Non c'erano differenze significative nei valori medi del diametro delle giugulari sinistre / destre, dopo il raggruppamento dei diametri giugulari in tre gruppi in base ai valori medi del campione ± deviazione standard. Le vene ≥10mm erano più presenti di quelle ≤6 mm. Una differenza significativa è stata trovata nei maschi vs le femmine inclusi nella voce "JSd≥10 mm" (30,7% contro 16,7%. X^2 = 22,9622 con df = 2 p <0,0001). Per quanto riguarda il gruppo "JSd≥10 mm", mentre nei maschi il rapporto Valsalva + / Valsalva- era di circa 1: 3, nelle femmine il rapporto era di circa 1: 2. Le femmine sono più anziane nel gruppo "JSd≥10 mm" vs soggetti di sesso femminile nei gruppi "1 <JSd <6 mm" o "6≤JSd <10 mm" (p <0.05: Kruskal-Wallis H prova = 8,0832 con df = 2). Le femmine di maggiore di età hanno un diametro giugulare più grandi delle femmine più giovani.
CONCLUSIONE: Dall'analisi dei dati, si può supporre che le femmine con CCSVI e SM presentano una meio-

pragia parietale, perché ci sono differenze significative nel rapporto Valsalva + / Valsalva- nelle femmine vs maschi inclusi nel gruppo "JSd≥10 mm" (circa 1: 2 contro 1: 3). Inoltre dilatazioni giugulari sono ugualmente presenti nel lato destro e sinistro e ciò può confermare l'ipotesi di una meiopragia parietale . La prevalenza della manovra di Valsalva + cresce con il diametro della vena giugulare, quindi si presume che la dilatazione della IJV sia legata alla presenza del reflusso giugulare. Ulteriori studi sono necessari per consolidare le nostre osservazioni.

References

1. Compston A, Coles A: *Multiple sclerosis.* Lancet, 2008 25; 372(9648):1502-17.

2. Zamboni P, Galeotti R., et al.: *Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis.* J Neurol Neurosurg Psychiatry, 2009; 80:392-99.

3. Lee BB, Baumgartner I, et al.: *Diagnosis and treatment of venous malformations consensus document of the international union of phlebology (IUP): Updated 2013.* Int Angiol, 2014.

4. Lee B, Laredo J, Neville R: *Embryological background of truncular venous malformation in the extracranial venous pathways as the cause of chronic cerebrospinal venous insufficiency.* Int Angiol 2010; 29:95-108.

5. Zivadinov R: *Is there a link between the extracranial venous system and central nervous system pathology?* BMC Med, 2013; 11:259.

6. Zivadinov R, Chung C: *Potential involvement of extracranial venous system in central nervous system disorders and aging.* BMC Med, 2013; 11:260.

7. Zamboni P, Morovic S, et al.: *Screening for chronic cerebrospinal venous insufficiency* (CCSVI).

8. De Burgh Daly M: *Interactions between respiration and circulation. Handbook of Physiology.* The Respiratory system, 1986; 2:569-70.

9. Porth CJM, Virinderjit SB, Tristani FE, Smith JJ: *The Valsalva maneuver: Mechanisms and clinical implications*. Heart Lung, 1984; 13:507-18.

10. Hamilton WF, Woodbury RA, Harper HT Jr.: *Physiologic relationships between intrathoracic, intraspinal and arterial pressures.* JAMA, 1936; 107:853-56.

11. www.ccsvi-database.it

12. Mandolesi S, D'Alessandro A, et al.: *Using the MEM-net program to report on mapping the EchoColorDoppler assessment for chronic cerebro spinal venous insufficiency.* Journal of Vascular Diagnostics, 2014.

13. Zamboni P, Sinisi F, Menegatti E, et al.: *An ultrasound model to calculate the brain blood out flow through collateral vessels: A pilot study.* BMC Neurol, 2013; 11:81.

14. Zamboni P, Consorti G, Galeotti R, et al.: *Venous collateral circulation of the extracranial cerebrospinal out flow routes.* Curr Neurovasc Res, 2009; 6:204-12.

15. Schaller B: *Physiology of cerebral venous blood flow: From experimental data in animals to normal function in humans.* Brain Res Brain Res Rev, 2004; 46:243-60.

16. Epstein HM, Linde HW, Crampton AR, et al.: *The vertebral venous plexus as a major cerebral venous outflow tract.* Anesthesiology, 1970, 32:332-37.

17. Valdueza JM, von Munster T, Hoffman O et al.: *Postural dependency of the cerebral venous outflow.* Lancet, 2000, 355:200-201.

18. Zamboni P, Menegatti E, Pomidori L, et al.: *Does thoracic pump influence the cerebral venous return?* Journal of Applied Physiology, 2012; 112:5, 904-10.

19. Chung CP, Hsu HY, Wong WC et al.: *Flow volume in the jugular vein and related hemodynamics in the branches of the jugular vein.* Ultrasound Med Biol, 2007; 33:500-505.

20. Akkawi NM, Agosti C, Borroni B, et al.: *Jugular valve incompetence: a study using air contrast ultrasonography on a general population.* J Ultrasound Med, 2002; 21(7):747-51.

21. Lepori D, Papasso P, Fournier D, et al.: *High-resolution ultrasound evaluation of internal jugular venous valves.* Eur Radiol, 1999; 9:1222-226.

22. Dresser LP, Mckinney WM: *Anatomic and pathophysiologic studies of the human jugular valve.* Am J Surg, 1987; 154:220-24.

23. Recek C: *Conception of the venous hemodynamics in the lower extremity.* Angiology, 2006; 57(5):556-63.

24. Bergan JJ, Pascarella L, Schmid-Schönbein GW: *Pathogenesis of primary chronic venous disease: Insights from animal models of venous hypertension.* J Vasc Surg, 2008; 47(1):183-92.

25. Silva MA, Deen KI, Fernando DJS et al.: *The internal jugular vein valve may have a significant role in the prevention of venous reflux: Evidence from live and cadaveric human subjects.* Clin Physiol, 2002; 22:202-05.

26. Wu X, Studer W, Erb T, et al.: *Competence of the internal jugular vein valve is damaged by cannulation and catheterization of the internal jugular vein.* Anesthesiology, 2000; 93(2):319-24.

27. Nedelmann M, Eicke BM, Dieterich M: *Functional and morphological criteria of internal jugular valve insufficiency as assessed by ultrasound.* J Neuroimaging, 2005; 15:70-75.

28. Zivadinov R, Marr K, Cutter G, et al.: *Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS.* Neurology, 2011; 77:138-44.

29. Schreiber SJ, Doepp F, Klingebiel R, et al.: *Internal jugular vein valve incompetence and intracranial venous anatomy in transient global amnesia.* J Neurol Neurosurg Psychiatry, 2005; 76(4):509-13.

30. Modabbernia A, Taslimi S, Ashrafi M, et al.: *Internal jugular vein reflux in patients with transient global amnesia: A meta-analysis of case-control studies.* Acta Neurol Belg, 2012; 112(3):2374-74.

31. Cheng CY, Chang FC, Chao AC, et al.: *Internal jugular venous abnormalities in transient monocular blindness*. BMC Neurol, 2013; 13:94.

32. Knappertz VA: *Cough headache and the competency of jugular venous valves.* Neurology, 1996; 46(5):1497.

33. Doepp F, Valdueza JM, Schreiber SJ: *Incompetence of internal jugular valve in patients with primary exertional headache: A risk factor?* Cephalalgia, 2008; 28(2):182-85.

34. S Furukawa, A Takaya, T Nakagawa, et al.: *Morphological variations of the internal jugular venous valve the internet journal of human anatomy.* 2010; 2:1.

35. Lewis SL: *Aetiology of transient global amnesia.* Lancet, 1998; 352:397-99.

36. Silverstein GE, Burke G, Goldberg D, et al.: *Superior vena caval system obstruction caused by benign endothoracic goiter.* Dis Chest, 1969; 56:519-23.

37. Peart RA, Driedger AA: *Effect of obstructed mediastinal venous return on dynamic brain blood flow studies: Case report.* J Nucl Med, 1975; 16:622-25.

38. Fred HL, Wukasch DC, Petrany Z: *Transient compression of the left innominate vein.* Circulation, 1964; 29:758-61.

39. Ferlini A, Bovolenta M, Neri M, et al.: *Custom CGH array profiling of copy number variations (CNVs) on chromosome 6p21.32 (HLA locus) in patients with venous malformations associated with multiple sclerosis.* BMC Med Genet, 2010; 11:64.

40. Niggemann P, Kuchta J, Grosskurth D, et al.: *Position dependent changes of the cerebral venous drainage-implications for the imaging of the cervical spine.* Cent Eur Neurosurg, 2011; 72(1):32-7.

41. Mandolesi S, Manconi E, Niglio T, et al.: *Incidence of anatomical compressions of the internal jugular veins with full block of their flow in patients with Chronic Cerebro-Spinal Venous Insufficiency and Multiple Sclerosis.* 21st Eurochap IUA –Roma 2013 Minerva Medica http://wm7.email.it/webmail/wm_5/redir.php?http://filesformailing.minervamedica.it/volumi/EUROCHAP.pdf

42. Coen M, Menegatti E, Salvi F, et al.: *Altered collagen expression in jugular veins in multiple sclerosis.* Cardiovasc Pathol, 2013; 22(1):33-8.

43. Sansilvestri-Morel P, Rupin A, Badier-Commander C, et al.: *Imbalance in the synthesis of collagen type I and collagen type III in smooth muscle cells derived from human varicose veins.* J Vasc Res, 2001; 38:560-68.

44. Haviarova Z, Janega P, Durdik S, et al.: *Comparison of collagen subtype I and III presence in varicose and non-varicose vein walls.* Bratisl Lek Listy, 2008; 109(3):102-05.

45. Rosch R, Klinge U, Si Z, et al.: *A role for the collagen I/III and MMP-1/-13 genes in primary inguinal hernia?* BMC Med Genet, 2002; 3(2).

46. Diaconu CI, Staugaitis SM, Fox RJ, et al.: *A technical approach to dissecting and assessing cadaveric veins pertinent to chronic cerebrospinal venous insufficiency in multiple sclerosis.* Neurol Res, 2012; 34(8):810-18.

47. Zamboni P, Tisato V, Menegatti E, et al.: *Ultrastructure of internal jugular vein defective valves.* Phlebology, 2014.

48. Pascolo L, Gianoncelli A, Rizzardi C, et al.: *Calcium microdepositions in jugular truncular venous malformations revealed by Synchrotron-based XRF imaging.* Scientific Reports, 2014.

49. Farina M, Novelli E, Pagani R: *Cross-sectional area variations of internal jugular veins during supine head rotation in multiple sclerosis patients with chronic cerebrospinal venous insufficiency: A prospective diagnostic controlled study with duplex ultrasound investigation.* BMC Neurology, 2013; 13:162.