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Echocolor Doppler morpho-functional study of the jugulo-subclavian confluence in chronic cerebro-spinal venous insufficiency and multiple sclerosis patients

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Echocolor Doppler morpho-functional study of the jugulo-subclavian confluence in chronic cerebro-spinal venous insufficiency and multiple sclerosis patients

OBJECTIVES: The aim of this work is to measure the mean diameter of the confluence jugulo- subclavian, the impact of different types of jugular confluences and the correlation between the types of confluences and the Valsalva maneuver (jugular reflux) in subjects with Chronic Cerebro-Spinal Venous Insufficiency (CCSVI) and Multiple Sclerosis.

METHOD: We investigated by Echo-Color-Doppler (ECD) 103 subjects (67 F 36M) of mean age 45 ± 12 years (a minimum of 22 to a maximum of 79 years, with a median of 44 and a modal value 42 years), mean EDSS of 4.7 and average disease duration of 12 years.

and average disease duration of 12 years. RESULTS: The 103 right jugular veins investigated had an average diameter of 8.4 ± 2.4 mm (minimum 4.0, maximum 14.9 mm; median 7.9; modal value 7.6 mm). Three form types were found: 56 cylindrical, 29 conical and 18 funnel. Valsalva maneuver was positive in 30 patients. The 103 left jugular investigated had an average diameter of 8.9 ± 2.4 mm (minimum 2.8, maximum 14.4 mm; median of 8.8; modal value 8.7 mm). The form types were found: 42 cylindrical, 45 conical and 16 funnel. Valsalva maneuver was positive in 30 patients.

CONCLUSIONS: The mean diameter of the jugular veins was 8.7 mm. Internal jugular veins with cylindrical morphology have a diameter smaller than other forms; this difference is statistically significant. The different morphology of the jugular vein confluence does not increase the possibility of a reflux because the positive Valsalva maneuvers are not statistically significant when compared to the various types.

KEY WORDS: CCSVI, EchoColorDoppler Map, Jugulo-Subclavian Confluence Diameter

Introduction

Chronic cerebro-spinal venous insufficiency (CCSVI), as has been claimed by Zamboni et al. ^{1,2}, is a pathologi-

cal condition characterized by difficulty vascular venous outflow from central nervous system and spinal chord due to stenosis or occlusion of extracranial veins, at the level of the internal jugular veins, vertebral veins and / or azygous veins. This anomaly of the venous outflow of the brain tissue seems to be the basis of the accumulation of iron in the cerebral perivascular tissue. Zamboni et al. have demonstrated that there is a high prevalence of CCSVI (about 71%) with the formation

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of a collateral circulation, in patients with multiple sclerosis who underwent echo color Doppler and/or venografy of the intracranial and neck vessels ³. Instead the study with color Doppler or venography of the intracranial and neck vessels in healthy controls, showed a low prevalence (about 7.1%) of CCSVI. These vascular lesions are frequently represented by segmental hypoplasia or intraluminal defects, generally classified as truncular venous malformations^{4,5}. 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 venous malformations such as aplasia, hypoplasia or hyperplasia of the vessels or it can cause the formation of malformed vessels for the presence of intraluminal obstruction or aneurysmal dilatation. The finding of an increased prevalence of abnormal venous drainage in patients with multiple sclerosis suggested that these vascular changes might be a contributing factor for the development and progression of this disease.

In order to make diagnosis of CCSVI Zamboni et al.² proposed sonographic criteria, which are listed below: *Criterion 1*: Reflux in the IJV and/or VV a) Bidirectional flow in one or both of the IJVs in both postures or bidirectional flow in one position with absence of flow in the other position. These findings suggest IJV stenosis; b) reversal or bidirectional flow in one or both of VVs in both positions. These findings suggest stenosis in the Azygos vein, based on reports controlling the Doppler parameter in comparison with catheter venography.

Criterion 2: Intracranial reflux

Criterion 3: IJV stenosis a) Severe reduction of the CSA of IJV in the supine position <0.3 cm2 which does not increase with Valsalva maneuver (performed at the end of the examination); b) intraluminal defects such as webs, septa or malformed valves combined with hemodynamic changes (increased velocity, absence of flow, reflux/bidirectional flow, etc). M-mode investigation of leaflets may clarify if they are mobile or not.

Criterion 4: absence of detectable flow in the IJV and/or VV Outflow obstruction in the cervical veins indicated by: a) absence of Doppler signal in the IJV and/or the VV, even after deep inspiration, in both sitting and supine positions or b) in one posture but with bidirectional flow detected in the other position. These findings are associated with stenosis proximal to the point of assessment.

Criterion 5: Negative difference of the cross-sectional area of internal jugular veins measured at J2 point (that is a change in the area between the supine and orthostatic hypotension).

In order to make a diagnosis of CCSVI must be satisfied at least 2 of the above criteria.

The aim of this study was to measure, in supine position, morphological and functional parameters of internal jugular veins with ECD: diameter of the confluence jugulosubclavian; incidence of various forms of confluence jugulo-subclavian; correlation between the different forms of confluence jugulo-subclavian and the Valsalva maneuver. Even if the routine is not recommended to perform the Valsalva maneuver for diagnostic evaluation of CCSVI, but in other circumstance it may be useful to view internal jugular veins. This is especially true in cases where in sitting position or in case of patients suffering from CCSVI internal jugular vein is completely collapsed for extra vascular compression. When venous vascular lumen expands by Valsalva maneuver and becomes viewable to the operator, that it is not a endo-vascular pathological condition, but if the light cannot be displayed using the maneuver this is a sign of hypoplasia, agenesis of internal jugular vein (IJV) or post thrombotic syndrome.

Methods

STUDY SAMPLE

We enrolled 103 patients with multiple sclerosis (MS) and CCSVI. This sample included 36 men and 67 women with mean age of 45 ± 12 years (a minimum of 22 years to a maximum of 79 years, with a median of 44 and a modal value 42 years). Among these, patients who were positive in two or more Zamboni's criteria, were suffering from CCSVI ².

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 in case the jugular-succlaveare confluence was deeper. The echografer used for the ECD was a My-lab Esaote Vinco. Patients were placed on a bed which was used to perform various measurements with the head positioned at 0° and 90°, first in the supine position and then in the upright position. Patients had to be able to cooperate during the fulfillment of the ECD. In fact, they were asked to perform Valsalva maneuver, and then making a push with the thorax keeping closed mouth and nose. This maneuver was performed to correctly identify the IJV and to evaluate the continence of venous valves. Has been performed an initial evaluation of the patency of IJV in transverse scan at the J2 level bilaterally. In this scan, and with the probe exactly perpendicular to the course of the vessel has been measured the area of the transverse section of the IJV at the medium level of IJV (J2). The comparison of the areas at 0 ° and 90 ° enables the assessment of compliance of IJV to the change of posture. Physiologically there is a positive difference by subtracting from the measured area in the supine position to the standing one. Conversely, a negative difference in area than or equal to 0 indicates a poor com-

pliance of the vessel, or a loss of postural control at the base of cerebro-spinal fluid drainage. Patients attempted Valsalva maneuver in orthostatic position and consequently we measured cross-sectional areas of internal jugular at J2 level. The evaluation of a positive or negative Valsalva maneuver was related to reverse flow which starts from jugulo-subclavian confluence upward until at least J2 point using ECD stud. Reverse flows have also been noted via inferior, middle and upper thyroid veins, but 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 terminals and pre-terminal valves of the internal jugular veins. We measured the diameters of the jugular-subclavian junction bilaterally, at supine position, this being the most suitable posture to fill most of the jugular veins. We measured diameters at the junction jugulo-succlaveare (D1) and 2 cm proximal to this last one (D2). The measure were made with a longitudinal cut and we chose the major cut to prevent measuring errors. We defined a confluence of cylindrical shape (F1) when D1 was equal to D2; a conical shape (F2) when D1 was greater than D2; funnel shape (F3) when D1 was less than D2.

STATISTICAL ANALYSIS

The data are given as mean values \pm standard deviation (SD), and categorical variables as frequencies and percentage. The linear correlation was assessed using Pearson's coefficient. Frequencies were compared using the Chi-square or Fisher's exact test. A P value of <0.05 was considered statistically significant. The statistical analyses were made by a member of the study group (PG) using Statistica 6.1 software (StatSoft Inc., Tulsa, OK, USA). Not parametric tests was performed by EPI-INFO software (Italian version 3.5.1 distributed by CDC Atlanta, USA).

Results

We had information about of EDSS value (Expanded Disability Disease Score) 6 only in 39 patients enrolled in this study, with a mean value of 4.7 ± 2.3 (with a

TABLE I - Duration of disease

minimum of 1 to a maximum of 9). We had instead information about of disease's duration of 47 patients with an average of 12 ± 10 years (from a minimum of 1 to a maximum of 50 years). The 103 right jugular examined had an average diameter of 8.4 ± 2.4 mm (from a minimum of 4.0 to a maximum of 14.9 mm, with a median of 7.9 and a modal value of 7.6 mm). The form types were found: 56 cylinder, 29 conical and 18 funnel shape. Valsalva maneuver was positive in 30 patients. The 103 left jugular veins examined had an average diameter of 8.9 ± 2.4 mm (from a minimum of 2.8 to a maximum of 14.4 mm, with a median of 8.8 and a modal value of 8.7 mm). We found three jugular shapes: 42 cylinder-like, 45 cone-like and 16 funnel-like.

Valsalva maneuver was positive in 29 patients. The difference of number of forms cylinder / cone between the right and left jugular is significant with Chi-square= 4.74and p= 0.0294277.

The 103 subjects can be divided by sex with these results: Female subjects (n = 67) of mean age 45 ± 11 years (a minimum of 22 to a maximum of 70 years, with a median of 42 and a 49 year old modal value): The 67 right jugular examined had an average diameter of 7.9 ± 2.0 mm (from a minimum of 4.4 to a maximum of 12.7 mm, with a median of 7.8 and a modal value of 6.3 mm). The jugular shapes were: 39 cylinder-like, 17 cone-like and 11 funnel-like.

Valsalva maneuver was positive in 20 patients. The 67 left jugular examined had an average diameter of 8.5 \pm 2.4 mm (from a minimum of 2.8 to a maximum of 13.3 mm, with a median of 8.7 and a modal value of 7.6 mm). The form types were found: 27 cylinder, cone 29 and funnel 11. Valsalva maneuver was positive in 20 patients.

Male Subjects (n = 36) of mean age 44 \pm 14 years (a minimum of 26 to a maximum of 79 years, with a median of 42 and a 42 year old modal value): The 36 right jugular examined had an average diameter of 9.2 \pm 2.8 mm (from a minimum of 4.0 to a maximum of 14.9 mm, with a median of 9.5 and a modal value of 7.4 mm). The jugular shapes were: 17 cylinder-like, 12 cone-like and 7 funnel-like.

Valsalva maneuver was positive in 10 patients. The 36 left jugular examined had an average diameter of 9.3 ± 2.3 mm (from a minimum of 5.4 to a maximum

EDSS_G	Pz	Mean	Std Dev			
123	13	8.0769	8.2104			
456	16	11.6250	11.3541			
789	10	21.6000	8.5661			
EDSS_G	Minimum	25%	Median	75%	Maximum	Modal
123	1.0	2.0	5.0	11.0	27.0	2.0
456	2.0	4.5	11.0	13.0	50.0	4.0
789	7.0	16.0	23.5	28.0	300	28.0

of 14.4 mm, with a median of 9.4 and a modal value of 6.7 mm). The form types were found: 15 cylinder, cone 16 and 5 funnel. Valsalva maneuver was positive in 9 patients.

The average diameters of the right jugular males were higher than females and it is statistically significant with Chi-square=5.04 and p= 0.0248.

If we analyze a stratification that takes into consideration the diameter of the jugular veins versus the shape of the confluence jugulo-subclavian we can observe that the morphology of the cylindrical type have a diameter less than the other forms and this difference is statistically significant.

If you look at the average duration of the disease stratified by EDSS score grouped we obtain the following The mean differences observed are statistically significant with a p-value = 0.0021. This shows that a longer duration of clinical disease corresponds to a worse EDSS score.

We performed detailed analyzes after stratification which, however, should be considered only for guidance for additional studies because the sample (after stratification) decreases considerably, thus affecting the absolute validity of the statistical tests. The analysis was performed on the duration of the disease in 26 patients with blockage of jugular stratified by EDSS score (Table II)

The mean differences observed are statistically significant with a p-value = 0.0047. It is recalled the low number of the analyzed samples that considerably reduced the discriminant power of the statistical test. In addition, an analysis was performed on the duration of the disease in 21 patients with jugular reflux stratified by EDSS score (Table III). The mean differences observed are statistically significant with a p-value = 0.0036. It is recalled the low number of the analyzed samples that considerably reduced the discriminant power of the statistical test.

It was not possible to perform analysis on the duration of the disease in only eight patients with compression of the jugular to shortage of the sample. Finally, an analysis was performed on the duration of the disease in 27 patients with stenosis of the jugular stratified by EDSS score (Table IV):

The mean differences observed are statistically significant with a p-value = 0.0233. It is recalled the low number of the analyzed samples that considerably reduced the discriminant power of the statistical test.

Discussion

The extra-cranial venous system is complex and variable between subjects and it is often asymmetric ⁷. Although venography is the gold standard for the study of the venous vessels, for the identification of anatomical location, type and extension of lesions causing CCSVI, the color Doppler (ECD) is a non-invasive, cheap and reliable exam for screening and diagnostic evaluation of patients with CCSVI and MS, as well as the study by Ciccone et al has shown ⁸.

Until a short time ago the extra-venous vascular abnormalities of the brain were considered as anatomical variants of development and were not considered as pathological findings ⁹. Over the last 10 years, the presence of reflux in the internal jugular vein, unilateral or bilat-

Table	Π

EDSS_G	Pz	Mean	Std Dev.			
123	5	7.2000	5.4037			
456	12	11.9167	12.9997			
789	9	24.1111	8.0381			
EDSS_G	Minimum	25%	Median	75%	Maximum	Modal
123	2.0000	3.0000	5.0000	13.0000	13.0000	13.0000
456	2.0000	4.0000	8.5000	12.5000	50.0000	4.0000
789	7.0000	22.0000	28.0000	30.0000	30.0000	30.0000
Table III						
TABLE III EDSS_G	Pz	Mean	Std Dev.			
TABLE III EDSS_G 123	Pz 6	Mean 6.5000	Std Dev. 8.0187			
TABLE III EDSS_G 123 456	Pz 6 11	Mean 6.5000 9.4545	Std Dev. 8.0187 4.6339			
TABLE III EDSS_G 123 456 789	Pz 6 11 4	Mean 6.5000 9.4545 26.2500	Std Dev. 8.0187 4.6339 4.3493			
TABLE III EDSS_G 123 456 789 EDSS_G	Pz 6 11 4 Minimum	Mean 6.5000 9.4545 26.2500 25%	Std Dev. 8.0187 4.6339 4.3493 Median	75%	Maximum	Modal
TABLE III EDSS_G 123 456 789 EDSS_G 123	Pz 6 11 4 Minimum 1.0000	Mean 6.5000 9.4545 26.2500 25% 2.0000	Std Dev. 8.0187 4.6339 4.3493 Median 2.0000	75% 11.0000	Maximum 21.0000	Modal 2.0000
TABLE III EDSS_G 123 456 789 EDSS_G 123 456	Pz 6 11 4 Minimum 1.0000 3.0000	Mean 6.5000 9.4545 26.2500 25% 2.0000 5.0000	Std Dev. 8.0187 4.6339 4.3493 Median 2.0000 12.0000	75% 11.0000 13.0000	Maximum 21.0000 15.0000	Modal 2.0000 6.0000

Internal jugular Venous Compression Syndrome: hemodynamic outcomes after cervical vertebral decompression manipulations

EDSS_G	Pz	Mean	Std Dev.			
123	14	7.6429	7.8994			
456	7	16.1429	15.5823			
789	6	19.1667	10.1669			
EDSS_G	Minimum	25%	Median	75%	Maximum	Modal
123	1.0000	2.0000	6.0000	10.0000	27.0000	1.0000
456	4.0000	5.0000	13.0000	15.0000	50.0000	15.0000
789	7.0000	8.0000	22.0000	28.0000	28.0000	28.0000

TABLE IV

eral, has been associated with several disorders of the central nervous system (CNS) ¹⁰⁻¹¹. Since Zamboni et al. have identified a correlation between the prevalence of CCSVI and multiple sclerosis, the involvement of abnormalities of the extra-cranial veins on CNS diseases and aging has been much discussion at this time ²⁴⁻²⁸. The hypothesis is that the venous blood flow slowed down or even reversed can cause damage to the central nervous system, upstream of the obstruction, and can start the process immune-mediated typical of MS ²³.

In particular CCSVI is a clinical condition characterized by abnormalities of the cerebrospinal venous outflow, such anomalies have been described at the level of the IJV, vertebral vein and azygous vein ⁹.

Zivadinov et al. ¹² provided an update on accurate informations about the anatomy, etiology and pathophysiology of anomalies and variants of development of the extra-cranial venous system. We can classify these vascular abnormalities in morphological / structural forms or hemodynamic / functional forms. Also we can distinguish between the morphological / structural forms that cause venous stenosis and / or occlusion and forms that cause anomalous venous relaxation; while we can distinguish hemodynamic / functional forms that cause abnormalities of cerebral venous outflow in forms with presence or absence of structural abnormalities of extracranial veins.

Beggs CB ¹³ hypothesized that an obstruction of the extra-cranial venous drainage may result in hypoxia phenomena in the CNS. In his study also claimed that for their hemodynamic properties peri-ventricular veins are particularly vulnerable to phenomena of ischemia and plaque formation, and this may explain their frequent involvement in MS. However, one of the most important indicators of "vascular origin" of multiple sclerosis comes from neuro-pathological observations that showed the presence of plaques that characterize MS in the perivenular and that the size of the veins are correlated with the shape, location, and the size of the lesions ^{14,15}. In case of a condition of CCSVI play an important role the emergence of collateral circulation for the venous blood drainage into the superior vena cava 16,17. Several studies have shown that the internal jugular veins have a physiological change in diameter in relation to different factors. In the first place 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 ¹⁸; 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.

the head during the performance of ECD ¹⁹. 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 complete compressions of the IJVs in front position are equally distributed in the various segments observed (J1, J2 and J3). 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 ²⁰.

In the study of Ciccone et al.²¹ has been demonstrated that young SM patients showed a statistically significant higher number of IJVs both hemodinamically and nonhemodinamically significant stenosis. Furthermore, youth showed a lower percentage of blocked outflow in the cervical veins than older patients. Patients >30 years old pointed out a significant higher degree of their clinical MS condition as well as their disease duration. No differences could be outlined about MS clinical form of disease. Young and adult group are different kind of patients, the former showing much more cerebral veins stenosis than the latter outlining blocked flow in IJV and vertebral veins. Duration of disease could explain such differences.

A careful analysis of the literature permits us to identify three different anatomical types of IJV: normal veins, veins with isolated valvular defects, hypoplastic veins. These last are described as small veins, with an area less than or equal to 6 mm² and with cylindrical aspect. ³. It was also demonstrated that there is a difference in size between IJVs left and right in the same patient; typically the IJVs left is smaller than the IJVs right ²².

Conclusions

In our study, we evaluated the morphological differences that exist between the sexes and depending on the seat right or left. The average diameter of the IJV confluence was 8.7 mm. The average diameter of the IJV right confluence in the male was higher compared to the female sex, and this difference was statistically significant. The IJV confluence with cylindrical morphology have an average diameter smaller than the other forms, this difference was statistically significant, also cylindrical confluence in both sexes is more frequent in patients enrolled in the study. Valsalva maneuver was positive in 30% of patients and not statistically significant when compared to the various types. The Valsalva maneuver outcomes highlight the hemodynamic result of this study: the different morphology of the jugular vein confluence does not increase the possibility of a reflux.

Riassunto

OBIETTIVO: Lo scopo di questo lavoro è quello di misurare il diametro medio della confluenza della Giugulare interna nella succlavia, l'incidenza delle diversi tipologie di confluenza e la correlazione tra queste e la manovra di Valsalva (reflusso in giugulare) in soggetti con insufficienza venosa cronica cerebro spinale (CCSVI) e la Sclerosi Multipla.

METODO: Abbiamo studiato con Echo-Color-Doppler (ECD) 103 soggetti (67 F 36M) di età media 45 \pm 12 anni (da un minimo di 22 ad un massimo di 79 anni, con una mediana di 44 e un valore modale 42 anni), media di edss 4.7 e media durata della malattia di 12 anni.

RISULTATI: le 103 vene giugulari destre avevano un diametro medio di 8,4 ± 2,4 millimetri (minimo 4,0, massimo 14,9 millimetri; mediana 7,9; valore modale 7,6 millimetri). Le tipologie trovate sono state: 56 cilindrica, 29 conica e 18 imbuto. La manovra di Valsalva è stata positiva in 30 pazienti. Le 103 giugulari sinistre avevano un diametro medio di 8,9 ± 2,4 millimetri (minimo 2,8, massimo 14,4 millimetri; mediana di 8,8; valore modale 8,7 millimetri). Le tipologie trovate sono state: 42 cilindrica, 45 conica e 16 imbuto. Manovra di Valsalva è stata positiva in 30 pazienti. La differenza di forme cilindriche su quelle coniche tra destra e sinistra è statisticamente significativa con Chi-quadro = 4.74 ep = 0,0294277. Nei maschi i diametri medi delle vene giugulari destre erano più grandi rispetto ai pazienti di sesso femminile e statisticamente significativi con Chiquadro = 5.04 ep = 0,0248.

CONCLUSIONI: Il diametro medio delle vene giugulari interne alla confluenza è di 8,7 mm.

Le giugulari interne con sbocco cilindrico hanno un diametro più piccolo statisticamente significativo rispetto alle altre forme. La differente morfologia della confluenza della vena giugulare non aumenta la possibilità di un reflusso in quanto le manovre di Valsalva positive non sono statisticamente significative rispetto ai vari tipi.

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