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Research Article

Assessment of chronic cerebrospinal venous insufficiency among Iraqi multiple sclerosis patients by Echo color Doppler sonography

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Abstract
Multiple Sclerosis (MS) is a chronic inflammatory disease affecting central nervous system in dissemination fashion, time and place. Immune pathophysiology is considered as the main underlying cause of MS since its original description. Recently, scientists hypothesized that chronic cerebrospinal venous insufficiency (CCSVI) is a potential cause of MS sparked a controversial discussion in the scientific communities. The aim of this study is to test this hypothesis by high resolution Duplex color Doppler sonography among Iraqi MS patient. Randomized cross sectional blind controlled study conducted on 42 Iraqi participants (23 relapsing remitting MS patients and 19 healthy controls) whom fulfilled the inclusion and exclusion criteria. All study participants were examined blindly with color Doppler and pulse wave Doppler. Chronic cerebrospinal venous insufficiency is assessed blindly according to Zamboni sonography criteria by expert sonographist. The examination performed in supine and sitting position with 5 minutes rest to reach a steady state. General gray scale ultrasound with 6-10 MHz linear probe was used for both sides of the neck to assess the followings: internal jugular veins (IJV) obstruction, state of jugular valves, measurement of cross sectional area of proximal part of internal jugular veins, assessment of blood flow whether present or absent and measurement time of reverse flow in both internal jugular and vertebral veins (VVs) during Valsalva maneuver (VM). CCSVI is considered positive in the presence of 2 or more of the Zamboni sonography criteria. There was no significant differences in all parameters and criteria of CCSVI between healthy control and MS study groups. In conclusion; this study concluded that CCSVI has no significant contribution in the pathogenesis of MS.

Key words: CCSVI; MS; Echo Doppler sonography and pathogenesis

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Introduction

Multiple sclerosis is an inflammatory and degenerative disease affecting central nervous system (CNS) in disseminated fashion time and place with broad spectrum signs and

symptoms [1]. It is the most common non traumatic cause of disability in young adults. The number of affected females are slightly higher than affected males and at a ratio of 3:2 with peak incidence rate was between18 and 50 years of age [2, 3] MS is most commonly affected people of European decent, less likely in Asian and rarely in black Africans. It has a prevalence that ranges between 2 to 150 per 100,000 [2]. Since the first description of MS in 1868 by Jean-Martin Charcot [3], the disease commonly regarded as an autoimmune disorder, although some phenomena associated with MS are difficult to explain on the basis of autoimmunity [4]. Recently, the topic of chronic cerebrospinal venous insufficiency (CCSVI) and its potential relationship to multiple sclerosis have been studied by several scientists 5-12 and generated tremendous interest in the news media, spilling over to MS patients and scientific communities. CCSVI was described as a state of chronic impaired venous drainage from the central nervous system (CNS) and Zamboni *et al* regarded it as a potential cause of MS when there is 2 out of 5 Echo colored Doppler (ECD) Zamboni criteria [5]. This was followed a small open-label studies conducted to evaluate the effect of endovascular angioplasty in MS patients with CCSVI, a procedure known as
"Liberation surgery [11, 12]. It has been hypothesized that CCSVI might lead to clinically overt Multiple sclerosis either due to activation an autoimmune reaction by cerebrovascular endothelium in the setting of refluxing blood flow [13], or due noxious activity of iron deposit which can be stored in brain parenchyma as a result of break down in blood brain barrier [14]. The discovery of so called CCSVI which comprise of stenosis and occlusion in the extracranial veins draining central nervous system, the azygous vein (AV) and internal jugular veins (IJV) have shed new light on potential cause of MS [15]. Although subsequent clinical research has failed to support this hypothesis [16-18], the debate currently continues over whether the relationship is real. Echo colored Doppler was widely used to assess CCSVI in MS [518]. Magnetic resonance venography (MRV) have been used with less sensitivity in detecting intraluminal jugular defects [19, 20] while venography was used by Yamout *et al* [21]. Our study conducted to assess any possible association between chronic cerebrospinal venous insufficiencies among Iraqi MS patients by using high resolution color Doppler sonography

Material and methods

A randomized case double blinded controlled study conducted between the months of February to August 2013 at Middle Euphrates Neuroscience CenterAn najaf city by including a total of 42 Iraqi study participants (patients and controls).

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Study group

They are including 23 patients with clinically defined MS (CDMS) selected randomly from MS clinic, All are diagnosed as relapsing remitting MS patients according to revised McDonald diagnostic criteria [22, 23], fifteen of them females and eight males and their ages ranged between 21 to 46 years old, with their disease duration ranging from 1 to 15 years. The degree of disability was assessed according to expanded disability status score scale [24] (EDSS) were ranged between 1-6 at time of study) and their mean Expanding Disability scaling system was 2.2826±1.657. One of the patient excluded from the study due to her hereditary hematological disorder (thalassemic patient). All patients were on Betaferon treatment.

Control group

Nineteen clinically healthy (HC) volunteers with age- and sex-matched (12 women and 7 men) were selected. The age of HC group was ranged between 18 years to 45 years. Both study and control groups signed consent and formal approval of the Medical Ethics Committee at the College of Medicine/University of Kufa were obtained.

Exclusion and inclusion criteria All study participants have to meet the inclusion criteria mentioned in the study group. Exclusion criteria include medical and surgical histories and anthropometric data recorded including age, history of cigarette smoking, cardiovascular disease, renal and hepatic disease, hypertension, diabetes mellitus, and current use of medications that affect our finding as confounders. Each participants was examined by ultrasound with color Doppler and pulse wave Doppler machine GE Vivid 3. The transducer is linear with 7.5 MHz, The Doppler sample volume was 2 mm, and the wall filter was 50–100 Hz. and the spatial temporal average intensity was 100 Mw /cm^2 according to manufactures specification. The examination was conducted blindly by the same expert radiologist. The participants were divided into two groups; group (A) represents the MS patients and groups (B) the healthy

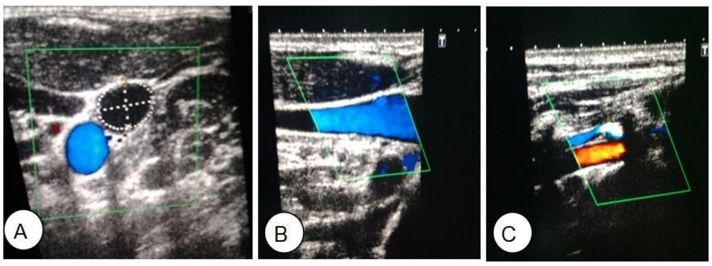

Figure 1.
(A) Demonstrate CSA of Left IJV, (B) flow in IJV of same patient taken in longitudinal view, (C) left vertebral vein (coded blue).

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controls. As shown in figure 1, the examination performed in supine and sitting position with 5 minutes rest after each examination to reach a steady state. General gray scale ultrasound with 6-10 MHz linear probe was used for both sides of the neck to assess internal jugular veins, state of jugular valves, measurement of cross sectional area of proximal part of internal jugular veins, assessment of blood flow whether present or absent and measurement time of reverse flow in both internal jugular and vertebral veins (VVs) during valsalva maneuver (VM) in both sitting and supine positions.

Assessment of CCSVI

In this study, an intensive effort was used to determine the presence of 2 or more of the following criteria by which CCSVI has been defined by Zamboni *et al* [5]:

1. Reflux in the IJVs and/or VVs in sitting and supine posture. In normal subjects, flow in the IJVs and VVs is directed toward the heart in any position of the head [25-27]. Reverse flow from its physiological direction for a duration of more than 0.88s regarded as pathological [28]. Flow was assessed during a short period of apnea following a normal exhalation [26].

2. High resolution B-mode evidence of IJV stenosis. We assessed the presence of proximal IJV stenosis by measuring the CSA of the IJV: a local reduction of the cross surface area CSA $\geq$ 50 % or a CSA $\leq$ 0.3 cm^2 in the recumbent position was defined as a stenosis [17].

3. Flow not Doppler detectable in the IJVs and/or VVs.

It was assessed by the lack of a Doppler detectable venous flow in the IJVs and/or VVs at four extra cranial venous drainage pathways despite numerous deep inspirations [26].

4. Reverted postural control of the main cerebral venous outflow pathway by studying differences in CSA in the IJVs, obtained by subtracting the CSA measured in the supine from that in the sitting position, it is a positive value in normal subjects [25, 26, 30, 31].

We assessed the occurrence of a negative difference in CSA value, representing the loss of postural control of the predominant outflow route in the supine position. Among 42 participants enrolled in the current study, 168 observations of bilateral internal jugular and vertebral veins criteria were calculated.

Statistical analysis

Using SPSS (statistical package for social sciences) version 20, in which we used independent sample T-test for measurement data and chi-square (X^2) for categorical data, we set P value <0.05 as significant.

Results

Basal characteristics of study and healthy control group all the 23 patients with clinically definite multiple sclerosis (CDMS) were with relapsing remitting MS. The ratio of female to male are

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1.9:1and their mean age 33.91± 8.40 years, mean duration of disease among patients was 5.21 ± 5.12 years with mean expanded disability scoring system (EDSS) was 2.28 ±1.65 as shown in table 1. Nineteen healthy controls fulfilled the inclusion and exclusion criteria and their mean age was 33.91± 8.33years, and female: male ratio was 1.7:1, as shown in figure 2.

Chronic cerebrospinal venous insufficiency parameters assessment 1- Internal jugular vein cross surface area

In MS patients; the mean CSA measured in supine position on the right side was 0.87 ±0.45 cm^2 and reduced to 0.31 ± 0.26cm^2 in the sitting posture, while it's mean CSA on the left side was 0.89 ±0.49cm^2 and reduced to 0.39 ±0.45cm^2 in the sitting position. In healthy control,

Table 1.
Basal characteristics of study and control group

Group	MS	HC
Subjects no.	23	19
Mean age, yr(SD)	33.91±8.40	33.91± 8.33
F/M	15/8(1.9:1)	12/7(1.7:1)
Mean disease Duration, yr(SD)	5.21±5.12	-
Mean EDSS Score(SD)	2.28± 1.65	-
Previous medical History	-	-
Smoking	-	-

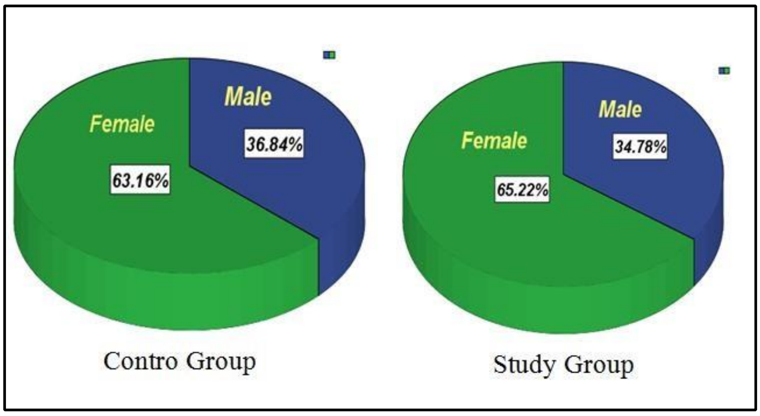

Figure 2.
Gender distribution among study and healthy control groups

the mean CSA in right side in supine posture was 0.95 ±0.54 cm^2 and reduced

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to 0.26 ±0.24cm^2 in sitting position. The left IJV mean CSA was 0.84 ±0.32 cm^2 and reduced in sitting position to 0.34 ± 0.22 cm^2. The results demonstrated that there is no significant difference in CSA between our MS patient and HC in any position and in any site, as shown in table (2). 2- Reflux in the internal jugular veins and/or vertebral veins in supine and sitting position.

Flows in IJVs and VVs were strictly normal and unidirectional, toward the heart in both MS patient and HC participants, reflux >0.88s was not seen in any one of the participants. 3- Evidence of IJV stenosis

The CSA ≤0.3cm^2 was found in the left IJV in one patient out of 23 in study group (4.34%), while it was normal in the right IJV.

Stenosis in IJV was found in 3 out of 19 of healthy control (15.78%), there were no significant differences between MS patients and healthy subjects with as shown in table 3.

4- Flow not Doppler- detectable in the internal jugular veins and/or vertebral veins.

Among control individuals, there were no flow in VV was detected bilaterally in one subject despite multiple deep inspiration while one MS-patient we found no flow in the right VV despite detectable lumen. The difference was

Table 2.

not significant between the groups as shown in table 3. Reverse postural control (i.e. CSA in supine –CSA in sitting) was found in 2 MS patient out of 23(2/23) and none was found in HC (i.e.0/19); P value found to be insignificant as shown in table 3. In conclusion: Using our dedicated Doppler Ultrasonic examination we found 3 out of 23 patient had only single positive criteria which represent (13%) of MS patients, while these criteria were found in 4 out of 19 of HC participants (21%). In general only one patient had 2 positive criteria i.e. only one patient fulfilled the definition of CCSVI.

Cross surface area of internal jugular veins between MS versus healthy control group

Variable	MS	HC	P value
	mean± SD(cm^2)	mean± SD(cm^2)	
CSA supine(RT)	0.87±0.45	0.95 ±0.54	0.613
CSA sitting(RT)	0.31±0.26	0.26 ±0.24	0.542
CSA supine(LT)	0.89±0.49	0.84 ±0.32	0.701
CSA sitting(LT)	0.39±0.45	0.34 ±0.22	0.664

Table 3.
The comparism between different CCSVI parameters in MS group versus control group

Variable		MS/N=46*	HC/N=38*	P value
Gender	Male	8	7	0.89
	Female	15	12	
IJVs stenosis Both sides	No stenosis	45	35	0.22
	stenosis	1	3	
Negative ΔCSA in IJVs (Reverse PC)	No	44	38	0.56
	Yes	2	0	
IJVs&/or VVs. Flow	Present flow	45	37	0.92
	Absent flow	1	1	

IJVs=Internal Jugular vein stenosis, VVs=vertebral veins,
Reverse postural control (^=difference CSA in supine –CSA in sitting)
* represent the number of veins checked but not the no. of patients; so we have 46 veins checked in 23 MS group and 38 veins checked in 19 control group.

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Discussion

The CCSVI hypothesis has provoked significant attention among scientific community, their after endovascular percutaneous Angioplasty was performed by several investigators as suggested by Zamboni and co-workers [11] as treatment for MS. This procedure was halted in many centers due to serious adverse events [32]. The hypothesis of CCSVI was tested by different studies using extra and transcranial sonography [33] others by using phase-contrast magnetic resonance imaging and contrastenhanced magnetic resonance angiography [34], Yamout *et al* studied CCSVIs by using selective venography [21]. This study intended to replicate the data presented by Zamboni *et al* [5], using exactly the same sonography protocol, with double-blinded controlled study design. Zamboni and co-workers investigated 65 MS-patients and 235 HC in a two-step procedure. First, screening was performed according to the 'protocol' described above [5]. In case of ≥2 criteria fulfilled by the patient, angiography was used. Because angiography was conducted unblinded, which affected the validity of the screening procedure and in turn affected the outcome of the validity of the whole study? In this study, the extracranial venous 'reflux' in the IJV and VV was the first parameter assessed, and we found no reflux in both IJV &/or VVs in both MS and HC groups. The validity of this threshold value is, however, questionable. It stems from a study on IJV valve insufficiency, where retrograde flowjets through insufficient valves were found to last >1.23s, while physiological backward flows during normal valve closure lasted 0.22-0.78s [28]. The threshold of 0.88s allows for discrimination between physiological reflux during valve closure and retrograde insufficiency flow. This was, however, assessed during a controlled VM, producing an entirely different physiological condition. In the Zamboni study no VM was applied [5]. The rationale for transferring this threshold, initially established to assess venous valve insufficiency to the unrelated context of CCSVI where it will serve to assess reflux without association to valve insufficiency remains unclear and is not scientifically sound; even more so as conditions of measurement were different by omitting VM. Furthermore, the 'Zamboni-protocol' does not require assessment of IJV-valves. This is another major shortcoming because IJV insufficiency is directly linked to the function of jugular valves [34]. Also, the incidence of jugular valve insufficiency reaches up to 29% in the normal population [28], whereas the incidence of MS is comparably very low, approximating 0.03%. Therefore, reflux in the IJV is 1000 times more likely to indicate insufficiency of IJV valves than MS, unless excluded by an experienced sonographist. While jugular valve insufficiency was shown to be linked to certain neurological disease entities, such as transient global amnesia and idiopathic intracranial hypertension [35, 36], and its direct pathological significance has not yet been established. It may likely to be viewed as non pathological phenomenon in a relevant proportion of human. Also our results regarding reflux criterion in contrast to both Simka *et al*, study (2010) [37] and Barachini *et al*, study (2011) [38] in which the incidence was 42.8% and 24% respectively. Our results were consistent with bothe Doepp *et al*, study (2010) [39] and Mayer *et al* study (2011) [40] where their results, 0 out of 56 patients and 0 out of 20 respectively. Regarding stenosis of IJVs, (applying CSA a cut off value of $\leq$0.3cm^2) IJV stenosis was present in one MS patient (4.3%) and in three healthy persons (15%), which is in contrast to previous published data (Zamboni *et al*, Simka *et al*, Barachini *et al* and Mayer *et al*). Zamboni reported stenosis in 37% of MS patients and zero in control group, while Simka, Barachini and Mayer reported stenosis in 87%, 16% and 65% respectively [37, 38, 40], and in 80% the healthy control group and indicated that there was no significant difference between both the patients and healthy control groups. While our results were consistent with those reported by Doepp *et al* [39]. Therefore, IJV-CSA $\leq$0.3 cm^2 seems unrelated to MS and may represent a common finding in both MS patients and healthy adults. Another limitation was in the assessing of 'stenosis' was solely based on IJV-CSA with its low specificity due to thin vessel walls, and by exerting mild pressure during examination by the ultrasound-probe inevitably alters vein diameter, and ultimately may lead to false-positive results. Doepp *et al* measured venous blood volume to avoid these problems found no difference between MS patients and healthy controls [39]. These considerations raise serious doubts as to whether the criterion of CSA $\leq$0.3cm^2 can be considered valid with respect to what it aims to measure.

Regarding 'lack of flow' in IJV and/or VV despite deep inspiration was considered to provide indirect evidence for stenosis, in the current study, this criterion demonstrated only in one participant in each group (4.3% in MS and 5% in HC) which is much lower than Zamboni findings where there was 52% stenosis in MS-patients and 3% in the control group, and Simka *et al* found 52.9 % in MS patients. Our results are consistent with those reported by Barachini, Doepp et al and Myer *et al* and they were 6%, 8.9% and 0% respectively [37-40]. The fourth screening parameter, a negative value of IJV-Δ*CSA (CSA supine-CSA upright)*, was claimed to reflect 'loss of postural control of the predominant outflow route in the supine position. In the current study, this criterion present in 2 out of 23 MS patients (8.6%) and none in control group (0%). Negative ΔCSA, however, reflects normal conditions in healthy subjects, as predominant outflow via IJV in the supine but via VVs in the upright position was typically found. Ultrasound-based investigation of vessels is known to be susceptible to rater-bias [7], which becomes an increasingly important issue, when venous signals with unfavorable signalto-noise-ratio are assessed. Therefore, blinding of sonography and rater (an average of at least two readings) to the study participants in patient *vs*. control group within a study-setting is crucial.

In our study, sophisticated blinding procedures were applied to assure the highest possible standards of our protocol. We found no evidence for 'venous congestion' in MS, despite adoption of the 'Zamboni protocol [5]. After ultrasound assessment, positive results were observed in all 65 MSpatients enrolled in their study, Zamboni and co-workers performed and rated venography in an unblinded manner, revealing 'stenosis' of the major venous conductors in variable locations in each patient but none was observed in the 235 controls [5]. This perfect association of 100% constitutes a very uncommon finding in biological systems, and therefore careful interpretation of those data is warranted [7-10]. The hypothesis of CCSVI raises further questions concerning conceptual plausibility [9]. In correlating four distinct topographical patterns of

'venous obstruction' detected in MSpatients with clinical course, Zamboni

List of abbreviations

MS: Multiple Sclerosis

et al stated a significant correlation (*P*<0.0001) between the pattern of bilateral IJV stenosis with both relapsing remitting Multiple Sclerosis (RRMS) (44%) and secondary progressive multiple sclerosis (SPMS) (56%) [5, 11] which suggested that bilateral IJV stenosis predispose for the development of MS. Evidence for higher incidences of MS in patients after bilateral neck-dissection, which would match complete bilateral IJV occlusion, is, however, lacking [41]. **In conclusion**; this blind case control study does not support insufficient extra cranial venous flow in MS. Our study with other recent studies [37-42]. All constitutes compelling evidence against a significant contribution of CCSVI in pathogenesis of MS.

Competing interests:

The authors declare that they have no competing interests.

CCSVI: Recently chronic cerebrospinal venous insufficiency
IJV: internal jugular veins
RRMS: relapsing remitting Multiple Sclerosis
VV: vertebral veins
CSA: cross surface area
VM: Valsalva maneuver
EDSS: expanded disability status score scale
CDMS: clinically defined MS
ECD: echo colored doppler
MRV: Magnetic resonance venography
CNS: central nervous system
AV: Azygous vein
HC: healthy control
RPC: Reverse postural control
SPMS: secondary progressive multiple sclerosis

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